WHITE PAPER

Continuous Flow - An Emerging Alternative

Dr Sripathy Venkatraman, Head of R&D operations at Curia, shares some insights on continuous flow processing as an alternative to conventional batch mode

Pharmaceutical companies have traditionally been very risk-averse and have adopted safe and well-established processes. This probably has its roots in the fact that the regulatory agencies in general have been very conservative and less approving of novel methodologies being used in the process unless absolutely necessary.

However, this is now changing. With the growing complexity of drug molecules and the need to involve newer and harsher reaction conditions that were once thought of as unfriendly in process chemistry, continuous flow chemistry and processing (figure 1) offer a proven alternative pathway.

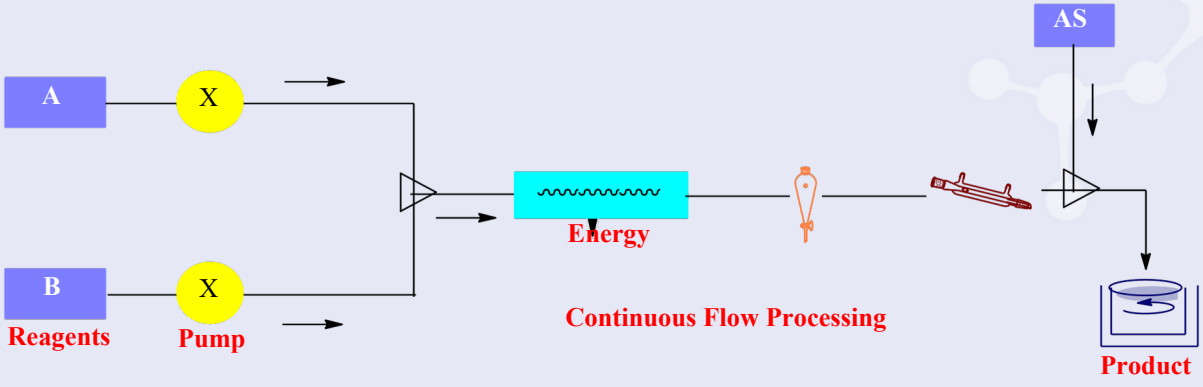

Figure 1 –Concept of continuous flow processing

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The last decade has also seen the growth of several companies providing commercial continuous flow units for research to large-scale production. Some of these, which are fully GMP-compliant and offer the ability to scale up rapidly have multiplied the interest in and access to continuous flow.

Until recently, continuous flow chemistry mainly focused on reaction chemistry and isolation largely followed a batch process. More recently, with the availability of lab-scale processing units, the concept of chemistry followed by continuous isolation of the product has seen growing interest.

Many fine chemical manufacturers with thin margins have used flow technologies to take advantage of the efficiencies continuous processing provides when batch mode would have been cost-prohibitive. With biotech companies turning more towards orphan indications and the shrinking appetite for traditional drugs, manufacturers have also been more receptive to the idea of alternative more selective options.

Increased competition from generic drug manufacturers and falling R&D productivity rates have forced pharmaceutical companies to find faster, more efficient ways of developing and manufacturing new products. Many companies have reduced in-house capacity and outsourced to CMOs in a bid to cut costs.

Initially, only basic manufacturing operations were outsourced. However, it is now common for a drug company to hand everything from discovery through clinical development and commercial production to a contractor. This demand for comprehensive services has driven consolidation in the sector, with large CMOs acquiring smaller specialists to expand and differentiate their offerings.

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Drug substance

In flow chemistry, substrates and reagents react in a highly reproducible environment where parameters such as heat and mass transfer, mixing and residence times are controlled. Reactors are customised for each reaction and are assembled from specialised components.

For API and Intermediate syntheses with reaction kinetics that are suited to continuous flow, there are numerous potential advantages over batch-based production. These can be split into three broad categories: quality, innovation and safety.

The US FDA requires APIs to meet purity specifications and manufacturers to implement systems for managing quality at each stage of production. Process safety information based on risk assessment not only helps in delivering safe operations but also ensures product quality when the parameters are out of normal operating range.

QbD

Continuous flow chemistry is also more in keeping with regulatory agency demands for precise, fully documented manufacturing processes. For example, the FDA and the European Medicines Agency (EMA) encourage drug companies to use quality by design (QbD) principles in which manufacturing processes are planned in a way to ensure that products are of the highest possible quality.

Again, batch operations can follow QbD principles. Critical parameters like temperature and pressure can be monitored and controlled in such systems. However, it is not normally easy to modify these parameters while the reaction is running, because doing so would potentially Invalidate the batch.

In contrast, parameters in a flow system can be modified while the process is running, with minimal impact. Any product impacted by out- of-specification parameters can be easily separated from the stream while the reaction continues. Furthermore, because continuous flow systems employ automated control processes and in-line monitoring technologies, any deviations likely to impact API quality can be rapidly detected and corrected.

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API innovation

API production is a physical process as well as a chemical one. To make an intermediate or an API, raw materials and reagents must be mixed in the correct quantities, In the correct conditions, for the right length of time. Controlling this process depends entirely on the vessel in which the reaction is conducted.

In batch production, reactants are mixed in a reactor-effectively a sealed tank -and only discharged when the reaction has run its course. Such reactors involve a one-time capital Investment, are simple to run and are straightforward to operate. They can be used for multiple reactions as long as they are cleaned after each use. In contrast, continuous flow reactors can be thought of as long tubes or plates Into which reactants are fed and products discharged continuously. Such reactors are custom-made or commercially available, and in most cases are dedicated to a particular intermediate or API.

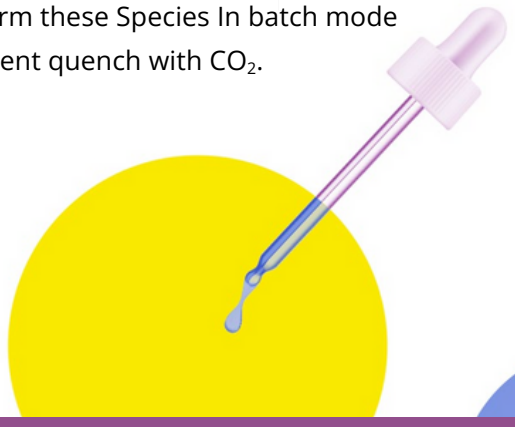
Continuous flow reactors have a number of advantages for API production, the foremost being the greater range of chemistries that are possible. Reactions that require micro mixing, or which use hazardous reagents, microwave energy, photochemistry, electrochemistry or sonochemistry are only possible in reaction chambers in which conditions can be precisely controlled.

For example, because of the small internal volumes and high surface-to-volume ratios in flow reactors, it is possible to conduct chemical reactions at higher temperatures and pressures more easily than can be achieved in batch reactions. Similarly, flow reactors allow for chemistries that require rapid mixing which is simply not possible in batch reactors.

Case Study

Curia developed a two-step carboxylation reaction of an aryl group. The process, which involves an anion formation, followed by a quench with gaseous CO_2 , was optimisedon a small scale using tubes and static mixers. The set-up was then used to process 21 kg of material in a regular lab with 88% yield.

The incorporation of a carboxyl acid to an aryl group by the addition of CO_2 to a Grignard or lithium anion is a well-known transformation that is widely used In chemical and pharmaceutical industries. While several major safety concerns have been reported at large scale for the formation of Grignard reagents or other organometallic species, it is still common practice to form these Species In batch mode with subsequent quench with CO_2.



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Most of these reactions are carried out at cryogenic temperatures, while temperature extrusions during CO_2 quench due to inefficient mixing often leads to several by-products.
Recently. there have been several reports on the generation of organometallic reagents and their subsequent additions to electrophiles under continuous flow conditions. These conditions offer a safe and efficient alternative to the current batch mode.

Compound 1 (Figure 2) is an intermediate used in the preparation Of an API. Several kilogram quantiles of this intermediate were required to support the production of the API for early phase work. It is reported that 1 was prepared by the addition of CO_2 to the lithium anion 3, which was generated from 2 at-78°C In 75% yield.

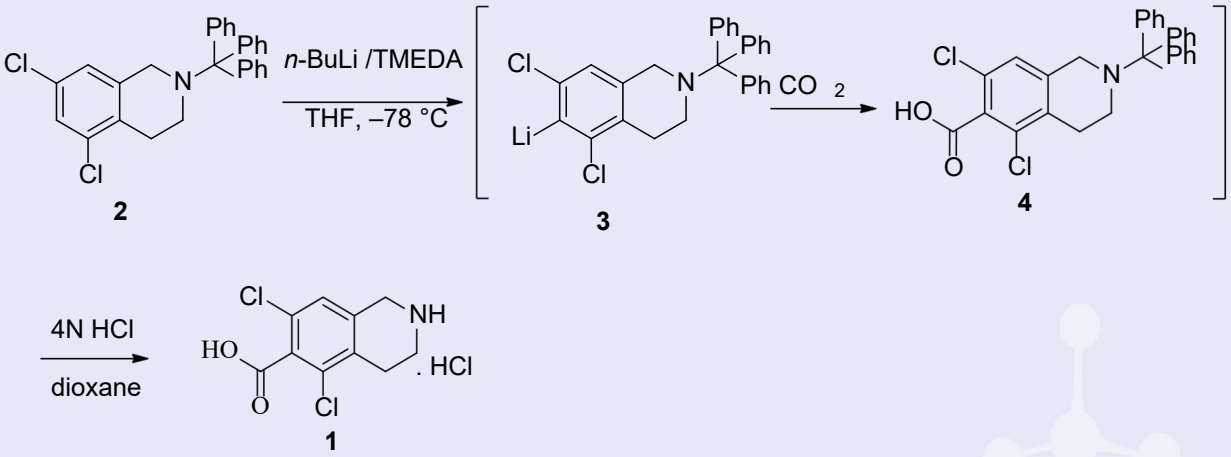

Figure 2 –Preparation of key intermediate

We found that the reaction's sensitivity to temperature and yields were much lower at larger-scale runs, with significant amounts of dark tar-like material isolated during work-up. In addition, several impurities were formed at higher (>-65°C) temperatures, due to the instability of the anion. Such uncontrolled reactions on a larger scale due to lack of sufficient heat transfer could lead to the formation of reactive benzyne-type intermediates, which polymerise violently.

We wanted to develop an improved process for the production of 3 using continuous flow chemistry. Our rationale for choosing it was based on four factors: ease of performing low-temperature reactions; high mixing of the gas-liquid phase; excellent heat transfer capacity under flow conditions; and consistent yield irrespective of the scale.

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Initial reactor design

Our initial concept of the reactor consisted of three loops (Figure 3 A, B and C) where A was used to cool a mixture of 2 and TMEDA in THE to -78'C (pictured). Just after A, the base was added and B provided the necessary residence time for the anion formation after which CO_2 was added as a gas which passed through C to give the product.

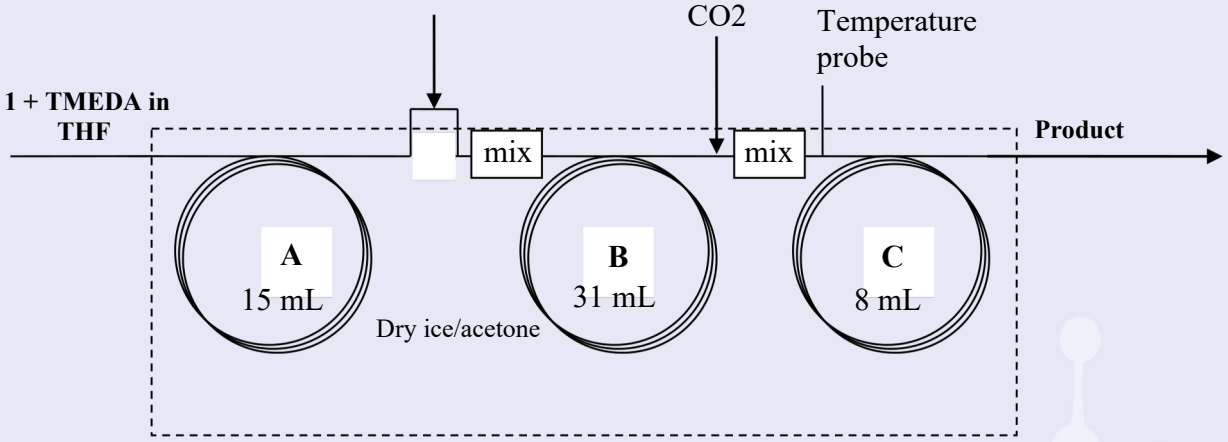

Figure 3 –Flow Reactor design during development

The entire reactor was submerged in a dry ice acetone bath. For the Initial design, the loops were made of 1.6 mm inch HDPE tubing with two HPLC pumps for the reagents. The mixing units consist of 6.3 mm ID diameter tubing with two small stir bars trapped within. The stir bars were agitated using a magnetic stir plate, providing turbulence sufficient for mixing of the reagents. The back-pressure unit at the end of the product stream was set to 0.7 bar.

The residence times for the trial runs were based on reaction monitoring in a batch mode (HPLC analysis). Interestingly, the addition of the base to 2 in THF is marked with a colour change frompaleorangetodark red,which decolorisesupon quenching. The flow rates were adjusted to achieve a base stoichiometry twice as high as the starting material.

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For the first few experiments, a small CO_2 cylinder was directly connected to the flow reactor. The product stream was collected after the steady stage was achieved and worked up in a batch mode by quenching with 2N HCI, extraction with ethyl acetate. and telescoping it to the subsequent reaction. After several such trial reactions, the parameters were optimisedand product-dependent parameters were understood.

For the scale-up batches, three stainless steel tubes, 8 mm in diameter were built, coiled and immersed into a carboy filled with dry ice acetone. Six static mixers were Inserted into the tubes after both the anion formation and CO_2 quench to provide the required mixing. Each batch was performed within one day and five such batches were sequentially carried out. Table 1 summarisesthe details.

Table 1: Details of Scale-Up Runs

Entry	Scale (Kg)	Residence Time (min)		Purity (% AUC)	Yield Over Two Steps (%)
		Anion Formation	CO2 Quench		
1	5.4	2.0		91.6	81
2	3.5	2.0	0.9	94.4	
3	5	3.6	1.6	97.2	88
4	4	3.6	1.6	98.2	91
5	4	3.6	1.6	97.8	

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Conclusion

Continuous flow chemistry offers quality, innovation and safety advantages for early-phase API synthesis. Developing flow processes requires a deep understanding of chemistry. Scaling them up entails engineering expertise. Doing both efficiently requires a full-service CMO with the infrastructure to support complex projects and the know-how to innovate.

ABOUT CURIA

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