Continuous Flow for APIs and Intermediates (Part 1 of 2)

A Cambrex webinar overview

The introduction of continuous flow processing has changed the way we conduct chemistry. The oil, solvent and polymer industries have extensively used continuous flow chemistry for decades. However, when considering the fine chemical and pharmaceutical industries, continuous flow chemistry has been primarily used when batch operations are deemed unsuitable or unsafe – and in particular, where high energy chemistry is encountered.

Historically, chemists have been reluctant to embrace continuous flow development, instead preferring to develop processes with test tubes and scaling-up to large volume reactors. This method is often at odds with colleagues who have a chemical engineering background as they are more comfortable with the concept of continuous flow.

Cambrex entered continuous flow processing due to its extensive background in high energy chemistry, specifically nitrations and nitric acid oxidations and dates back to Alfred Nobel in 1896. As a result of their experience in this field, Cambrex will discuss the topic of continuous flow through two webinars.

This webinar will:

- Provide an introduction to continuous flow processing
- Provide a brief history of continuous flow at Cambrex
- Discuss the obstacles to be solved and overcome when implementing continuous flow
- Conclude with a brief look at the future of continuous flow

Contributors

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Continuous flow: Where chemistry meets engineering

In the pharmaceutical manufacturing sector, batch production has been the traditional workhorse of the industry whereas historically, continuous flow chemistry was reserved primarily for high energy, hazardous reactions. More recently, and driven by the availability of new technologies and equipment, there has been a growing movement towards continuous flow operations. Jonathan Knight, VP of New Product Development discusses the reasons behind this trend, together with a recent industrial example where Cambrex replaced a batch process with a continuous flow process, described by Fredrik Stenberg, Product Manager.

Continuous flow chemistry has traditionally been used by the API manufacturing sector only when batch operations were considered too dangerous: it was, and remains, a safe way of dealing with high energy products and reagents. Batch operations were carried out in bunkered production facilities located well away from main manufacturing areas with vessel sizes and inventories being kept deliberately low, so that in the case of an uncontrolled event any damage could be easily contained and the risk to personnel and the surrounding area would be limited. However, these restrictions meant that the cost of setting up and maintaining these facilities, together with the small scale of the reactions, was prohibitive.

A focus on continuous flow

Cambrex had considerable historical experience in continuous flow commercial operations at its site in Karlskoga, Sweden, including a simple, small, dedicated pump nitration facility which produced 300 tons/year of ortho-nitro benzaldehyde; and a dedicated nitric acid oxidation facility that produced more than 2,000 tons/year. In the early years of the 21st century the company looked to expand its development capabilities in continuous flow chemistry capabilities, however, the lack of suitable commercially available equipment became a significant obstacle. Micro reactors were available on the market but their inability to handle solids meant that they lacked the versatility required for developing the technology.

One solution was for Cambrex to design and build a bespoke continuous flow kilo lab facility, which had the option of being heated conventionally with a plate reactor, or by using a microwave heating system. The CaMWave kilo reactor proved very versatile, able to handle up to 10 wt% solids and capable of temperatures up to 200°C and pressures up to 20 bars, with the main reaction taking place in a 1 meter long, 5mm diameter quartz tube.

Since this time, the requirement to develop drugs faster, more cost-effectively and for smaller patient populations has lent

new impetus to the drive towards replacing batch production with continuous flow. A number of large pharmaceutical companies have invested in continuous flow operations for API production as well as formulation or both. For example, GSK has invested in continuous flow API development capabilities in its facilities in the UK, US and Singapore, while Vertex and Johnson & Johnson have both invested in continuous flow formulation technology, and Novartis, in collaboration with Massachusetts Institute of Technology (MIT), is looking at a combination of continuous flow synthesis and continuous flow formulation.

Cost, quality and safety

There are five main areas where continuous flow chemistry offers clear benefits over the more traditional batch operation: cost savings, quality improvements, scale up and scale out, safety and the ability to handle new technologies and reagents.

In terms of cost, the most striking difference between continuous flow and batch production is the comparative investment cost for a new plant, with the rebuild of a batch facility costing up to four times more than the expenditure on a comparable continuous flow facility. Additionally, continuous flow requires less labor and may lead to fewer analytical procedures, representing a reduction of up to 20% in operating expenditure.

For a process that is well understood and tightly defined, control can be maintained with simplified measurements. In such cases, the process analytical technology (PAT) required is generally easier than that of batch production – often with only temperature probes and flow meters being required to ensure that the process remains within the acceptable parameters (i.e. defined process window) to afford product of a known quality. If desired or necessary, sophisticated PAT probes can be easily integrated into a flow process to allow for rapid detection of deviations, in addition to nearly continuous monitoring of instantaneous quality, as opposed to waiting on a single batch sample and corresponding measurement.

Energy consumption can be cut by up to 30%, while solvent usage will also be reduced significantly, or in some cases, eliminated entirely; less waste solvent will also be produced which reduces costs associated with its disposal. Furthermore, the footprint of a new continuous flow facility can be less than half that required by a traditional batch operation.

Another important benefit is improved quality of the final product as the process can be designed to avoid or minimize the formation of impurities and analysis can be integrated into the process rather than functioning as a separate operation. Scaling up (or scaling out) is also easier and more cost-effective with continuous flow, as rather than having to transfer the process from a small reactor to a larger one and the validation requirement this entails, scaling up a continuous flow process simply requires the addition of another reactor of the same size to run in parallel alongside, thereby reducing validation costs significantly.

It is still the case today that continuous flow operation is the best and safest way of handling energetic and hazardous reactions. However, by enabling these operations to take place in a regular manufacturing plant they can be linked more directly to the other downstream processes giving the advantage of integration of operations. Finally, certain technologies such as photochemistry and electrochemistry do not lend themselves to batch operations, but are easily facilitated in continuous flow.

Case study: Development of a continuous flow nitration

All these benefits are demonstrated in the following case study, in which Cambrex took an existing batch operated nitration process from its existing bunkered facility at its Karlskoga site and turned it into a commercial scale continuous flow process with an annual capacity of more than 50 tons within its regular production facility. In doing so, it would not only increase capacity to meet growing demand from the customer, but also free up capacity as well as reducing operational costs.

The project presented a number of major challenges. The intermediate itself is high energy (more than 2,000 kJ per kilogram) and to transfer it into a regular manufacturing facility involved rigorous safety assessments and precautions. Additionally, the nitration reaction is exothermic and requires high cooling capacity to strictly control the temperatures during the reaction.

A further and more considerable challenge is the fact that the process is a heterogeneous liquid/solid slurry system - carrying more than 30% of the solid throughout the process from the raw material feed into the nitration reaction, followed by a quench step and isolation. Both heat and mass transport have to be managed carefully to achieve a safe and predictable operation of the process.

A further process requirement was to keep the purity profile unchanged as any variation could affect both capacity and quality in the downstream processes. Early development work in the laboratory used two reactors in series with peristaltic pumps both for feed and transfer between reactors. Due to the high level of solids in the system, continuous flow tank reactors were chosen to provide intense agitation. A high shear mixer disperses the solids in the feed to get a homogenous and smooth slurry, thereby reducing the risk of sedimentation and aggregation between the vessels, as well as reducing the particle size in the feed. After the homogenization of the feed, the high sheer mixer was used in the nitration reactor to maintain a homogenous slurry in the reaction as well.

Design of Experiments study (DoE)

A Design of Experiments (DoE) study was performed to investigate the impact of residence time and reaction temperature on yield and purity. The conclusion was that a long residence time and a high temperature are favorable for all responses and that complete conversion was achieved after only 10 minutes at any temperature above 40°C. Based on the DoE results and the lab experience, the design of the nitration reactors began, focusing on maximizing heat and mass transport. Two continuous flow stirred tank reactors of 15 liters each were chosen so that at any single time in the process the amount of material in each reactor was limited to 5 kg. The arrangement also offered a relatively high surface

Figure 1

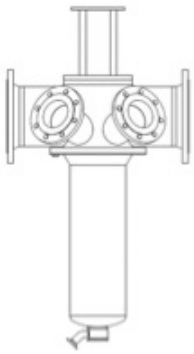
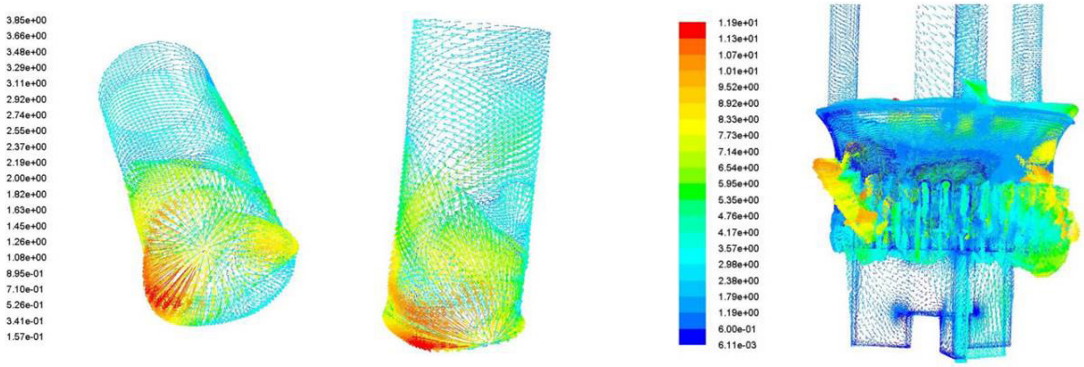


Figure 2



to volume ratio, which is beneficial for the heat transfer. To minimize the risk of any pressure build-up in the event of a runaway reaction, the design of the upper part of the overhead of the reactors was oversized. (fig 1)

In collaboration with the customer, the design of the reactor also took into account the fluid dynamics in the reaction cell. Based on the reactor and high shear mixer blueprints, the mass transfer profile was investigated and showed a good and intense mixing in the reaction cell at 1,500 rpm. (fig 2)

As previously mentioned, moving the process into a regular production facility required close attention to the safety aspects. As the product has a high energy content and an onset temperature (the temperature at which the heat that is released by a reaction can no longer be completely removed from the reaction vessel) of 85°C, there needed to be high cooling capacity in the reaction vessels to mitigate any risk of that temperature being reached. Also, using small reactors in series limited the amount of product present in each reactor and thereby the amount of energy stored at any one time.

Furthermore, to minimize the risk of explosion, the stoichiometric ratio between the substrate, the solvent and the nitrating agent had to be controlled by interlocking the control system, and by monitoring and controlling the ratio between the two feed streams into the nitration reaction. In an event where the temperature cannot be controlled, an emergency quench is available by means of a pre-pressurized tank that can release water into the nitration vessel. And as an additional level of safety, even if all these measures were to fail, the equipment is designed to withstand gas evolution of a complete decomposition of the reactants in the vessel.

Commissioning the production train

Commissioning of the new continuous flow nitration production train began within seven months from the start of the project. The equipment was first tested using water to verify the functionality, after which 14 pilot batches of varying size were produced to adjust process parameters during start-up, steady state and batch end. All 14 batches met the quality specifications, proving the robustness of the continuous flow process.

During commissioning, it was found that the product tended to stick to the reactor walls, mainly on the upper part of the first reactor. The fouling increased over time and had a negative effect on the cooling capacity, which limited the run time of a batch. A short intermediate cleaning procedure was introduced, but this reduced the capacity and throughput of the first trial. The solution was to add another reactor, which doubled the capacity of the production train for a relatively modest 10% additional investment.

The upgraded production train now consists of two nitration reactors working in parallel and with one confined post-reaction vessel. Capacity has been increased significantly and the capacity bottleneck has been moved downstream in the process to the product isolation and waste handling.

The fouling issue was resolved by improving the agitation profile in upper part of the reactor and by installing two additional impellers to boost the mass transfer.

The project has met all its target objectives. The annual capacity of the new continuous flow production train is in excess of 80 MT – well above the original target of 50 MT – and capacity has been freed up in the bunkered high energy pilot plant. More than 270 batches have now been produced, all of which are within specification and have the same purity profile as product made in batch mode. Furthermore, the improved repeatability in the continuous process generates product with a much more consistent quality between batches, compared with the previous process.

The safety of the process has been maintained and even improved, enabling operation in the regular production facility. This consolidation has, in turn, significantly reduced the overall cost of production and improved internal logistics.

Applications of multi-step continuous flow in early molecule development

This case study demonstrates the economic and safety benefits of implementing continuous flow retrospectively on a commercial scale for a single process step. However, there is an emerging use of continuous flow processes in early clinical development when the route of synthesis is designed for continuous flow.

Professor Steven Ley's group from Cambridge University in the UK carried out a study as early as 2006 that showed the seven-step synthesis of a natural alkaloid carried out as a continuous flow operation, including continuous flow work up.[1] This was achieved without the need for distillation, crystallization or column chromatography and gave an impressive 40% overall yield. As the route is complicated and contains some hazardous steps, including the use of azide and hydrogen, it lends itself to continuous flow operation.

Other companies are starting to design new processes that are suitable for continuous flow operation and are using them in early stage development and work up. Eli Lilly, for example, has started to use continuous flow technology in the production of clinical trial materials using a dedicated continuous flow team, and the final four steps in the development of the company's highly potent oncology drug, Prexasertib,[2] take place in continuous flow equipment. The process was originally developed for phase 1 clinical trial material but is now in use for commercial production at a rate of 3 kg a day, saving significant time and money during the development and scale-up phases.

Future developments

The current installed infrastructure in API manufacturing means that batch operation will continue to be the predominant production method for the foreseeable future. However, the interest from large pharmaceutical companies becoming increasingly engaged with continuous flow technologies, in both API manufacture and formulation, indicates that demand for continuous flow is set to increase. But key to its future will be a collaborative approach between the chemist and the engineer and the education to encourage the industry to move away from a batch mindset.

Laboratory chemists typically start off with small glass flasks and the flasks get larger and larger in volume as development progresses. Chemical engineers, on the other hand, have spent a lot of time studying continuous flow processes, and the important step for companies is to form dedicated continuous flow teams consisting of chemists, chemical engineers and analytical chemists to integrate skills, experiences and expertise to maximize the chances of a project's success. As with every new technology and application, the more case studies that are published, the greater the likelihood the industry will see the potential benefits and start to look positively at the promise of continuous flow chemistry.

References

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2 Kilogram-scale prexasertib monolactate monohydrate synthesis under continuous-flow CGMP conditions Kevin P. Cole Science 16 Jun 2017: Vol. 356, Issue 6343, pp. 1144-1150