WHITE PAPER

Continuous flow chemistry (processing) for intermediates and APIs

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Abstract

Many contract manufacturing organizations (CMOs) offer continuous flow chemistry, but few have the technical capabilities to help customers take full advantage. The potential benefits for active pharmaceutical ingredient (API) development and manufacturing include higher selectivity, the ability to use novel chemistries, improved scalability and enhanced safety. However, developing flow-based manufacturing processes requires expertise in several disciplines, the ability to design and build custom reactors, and the scientific infrastructure to support production. It also takes expertise to ensure continuous processes meet with regulatory requirements. Knowing how to define a "batch" of API calls for deep knowledge of the rules that govern drug manufacturing and development.

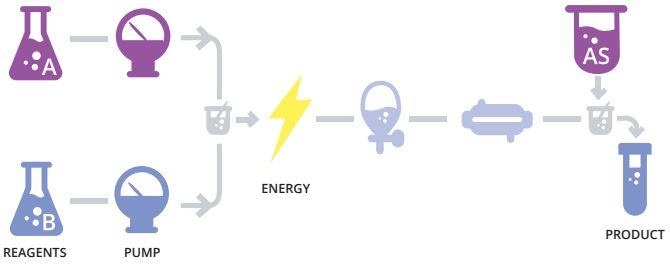
Introduction

Traditionally, pharmaceutical firms have preferred to make API and finished dosage forms in batches.[1] The batch approach, which splits unit operations into discrete steps, provides a way of reducing capital costs by allowing manufacturing lines to be used to make several products. It also suits the longer timelines and volume-focused sales strategies employed by the drug industry over the past few decades.

But times have changed. 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. Outsourcing, paying a third party to perform research or manufacturing, has been readily embraced by the industry. 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 of the contract manufacturing sector, with large CMOs acquiring smaller specialists to expand and differentiate their offerings.

Figure 1:
Schematic of a Continuous Flow Processing



One common CMO strategy is to offer innovative techniques like continuous flow chemistry in a bid to win business from pharmaceutical companies whose desire for efficiency is undiminished. But continuous flow chemistry is more than just a business strategy. It is a highly technically challenging form of manufacturing that requires expertise in a wide range of scientific disciplines and an infrastructure capable of supporting production. This white paper will examine the benefits and advantages of flow chemistry for API production. It will explain why it is important to undertake such projects in collaboration with a CMO that has the capacity to handle this more technically challenging form of manufacturing.

Advantages of flow chemistry

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 customized for each reaction and are assembled from specialized components. For API/intermediates syntheses with reaction kinetics that are suited to continuous flow, there are numerous potential advantages over batch-based production. These benefits can be split into three broad categories: quality, innovation, and safety.

API quality

Drug safety depends on API quality. A poor-quality medicine is usually less effective because it contains impure ingredients that pose a threat to health, which is why regulators insist pharmaceuticals meet strict quality standards. The U.S. Food and Drug Administration (FDA) requires that APIs are as pure as possible and that manufacturers implement systems for managing quality at each stage of production.[2]

Batch processes have been used to make APIs that meet such requirements for decades. However, it is increasingly recognized that quality, consistency and purity are easier to control in flow-based production.[3] For example, in batch syntheses, raw materials must be discharged from each process before being transferred to the next. These delays mean reactants can overreact and products can degrade, potentially reducing the quality of the final product or creating waste. Continuous flow avoids such problems. The product from one stage of the process flows simultaneously into the next and has no time to degrade.

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Quality-by-design

Continuous flow chemistry is also more in keeping with regulatory agency demands for precise, fully documented manufacturing processes. For example, the U.S. 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 products are of the highest possible quality.[4]

Again, batch operations can follow QbD principles. Critical parameters like temperature and pressure can be monitored and controlled[5] in such systems. However, it is not normally easy to modify these parameters while the reaction is running, as doing so could 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.[6]

Furthermore, because continuous flow systems employ automated control processes and in-line monitoring technologies, any deviations that are likely to impact API quality can be rapidly detected and corrected.[7]

API innovation

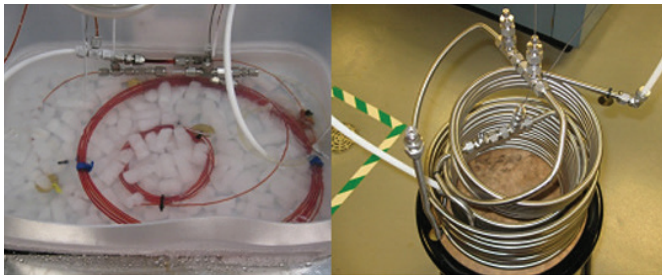
In addition to being a chemical process, API production is a physical process. To make an intermediate or an API, raw materials and reagents must be mixed in the correct quantities, in the correct conditions and for the right amount of time. Controlling this physical process entirely depends on the vessel 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, simple to run and straightforward to operate. They can be used for multiple reactions as long as they are cleaned after each use.

In contrast, continuous plug flow reactors can be thought of as a long tube into which reactants are fed and products discharged continuously. Such reactors are custom-made and in most cases dedicated for a particular intermediate or API. But despite this, continuous flow reactors have a number of advantages for API production over batch reactors, foremost of which is the greater range of chemistries that are possible. Reactions that require micromixing, or 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 are simply not possible in batch reactors. Initial development of a continuous flow process can start in a regular lab with smaller tubes and mixers. The concept and engineering depends on the expertise of the organization in design and process knowledge. During the initial research stage, the chemist/engineers can develop a proof of concept model (Figure 2) which can be modified for larger-scale operation. Ability to develop initial stage continuous flow processes in the lab is critical to larger continuous flow operations.

Figure 2: Model flow reactors during development



Safety

There are also safety advantages associated with continuous flow reactions. In general, reactors used in continuous flow chemistry have a smaller footprint than batch reactors. This means that, in the unlikely event of a runaway type situation, the damage to equipment, material and environment is limited.

The smaller reactors allow for the installation of real-time monitoring technologies that can rapidly identify any problems. Furthermore, the automation that underpins such systems can be used to implement automated shutdown procedures. Reaction volumes are also much lower in continuous flow than in batch systems. This means that chemistries requiring hazardous reactants or reagents that are too dangerous to attempt in a batch reactor can be conducted much more safely.[9]

Choosing a CMO

The potential quality, innovation and safety advantages of continuous flow for API production are clear. However, as has been previously stated, the complexity of developing and implementing such processes requires expertise. Therefore, it is important that pharmaceutical companies seeking a CMO for flow-based API production consider a number of factors.

The concept of continuous flow chemistry has been around for decades, emerging first in academic research employing micro-reactors for laboratory-scale development.[10] However, until recently, the cost and technical challenges involved in developing continuous flow chemistry-based production systems had meant the approach was rarely used for commercial API production.[11]

This has changed, and the pharmaceutical industry is showing renewed interest in flow chemistry for API production.[12] Partly this change has been driven by growing complexities in drug candidate structures and the need to utilize chemical transformations which, historically, were not considered usable in a batch mode. In addition, a growing need to improve product quality and cut costs heavily contribute to embracing such newer technologies.

However, increased competition among CMOs has prompted leading contractors to invest in technical capabilities to differentiate their offerings from rivals and has made flow chemistry commercially viable. For example, unlike batch reactors that are built from materials capable of withstanding the limited range of reactions employed in commercial API production, continuous flow reactors are custom built to suit the chemistry. Consequently, continuous flow reactors can be made from a much wider range of materials, including everything from copper and polytetrafluoroethylene (PTFE) to hastelloy and glass. Choosing the optimum material requires considerable engineering expertise.[13]

Speed to market is a key focus for the pharmaceutical industry. The sooner a new API can be tested, the earlier it can be submitted for regulatory review and – if approved – the sooner it can start generating revenue for its developer.

As a result, the focus at the earliest stage of drug development is on producing the API candidate quickly. What is often overlooked is that developmental production processes will need to be scalable. This means that a detailed understanding of various parameters is needed from the very earliest stages of production.

Engineering expertise is key. Having the capabilities to construct reactor trains and to assess critical process factors like mass transfer, heat transfer, distillation and drying is key to predicting whether a continuous process can be scaled-up for commercial production.

Expert staff

To develop a continuous flow process, a CMO needs staff with expertise in multiple scientific and engineering disciplines. Contractors with links to academic institutions are best placed to be able to hire technicians with the range of skills they need to keep up to date with emerging science. Therefore, when choosing a CMO, customers should check for both links with academia as well as a contractor's willingness to update staff skills.

Customers also need to ensure the CMOs that they work with have the resources to dedicate staff to complete each stage of the project. Timelines vary, but even initial feasibility studies can take two to three weeks, and they involve the development of custom reactors. Contractors with the capacity to dedicate sufficient staff are best placed to complete them in an efficient and timely manner.

Integrated support

As mentioned previously, developing a continuous flow process development involves multiple scientific and engineering disciplines. Whether creating a process from scratch or converting a batch reaction, the range of expertise required is considerable.

But the effective development of a flow process requires more than chemistry expertise. The ability to integrate a range of technologies in an efficient manner is also critical, which means that the most effective CMOs are those that have invested in in-house engineering, safety and analytical expertise.

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Similarly, an effective analytical department is a must-have for any serious CMO. Developing the methods for in-process conversions, release of intermediates and the API is highly complex and specialized, and it is best achieved when process development chemists can work with analytical scientists directly.

Conclusion

Continuous flow chemistry offers quality, innovation and safety advantages for early and late phase API synthesis. Advantages offered by flow chemistry justify the investment needed for specific processes for commercial production.

Developing the flow processes requires a deep understanding of chemistry. Scaling-up such processes requires engineering expertise. Doing both efficiently requires a full-service CMO with the infrastructure to support complex projects and the know-how to innovate.

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