PEER REVIEWED

Continuous API Manufacturing – It's Time to Go with the Flow

There has been a recent surge in interest in using more continuous processes in the pharma industry as the benefits have become more widely known. This is due to the availability of more expertise in the area of flow chemistry over the last decade, in combination with the need for the industry to develop safer, faster and more sustainable processes, with higher quality and less expensive products. But the first thing we need to do is define what we mean by continuous processing and flow chemistry. The industry is running two broad types of continuous processing, in finished formulations and API manufacturing – often commentary in the media has made little effort to separate these, and they invariably get confused. Whilst continuous processing in finished formulations with the potential of on-demand dosing is extremely exciting, for the purpose of this article we are instead going to specifically look at the improvements flow chemistry can bring to process development and manufacturing for APIs.

It is time the wider pharma community set aside the decade-old views of continuous manufacturing as a 'luxury but impractical tool' and looked at the technology as a practical and valuable approach that can resolve our everyday chemical processing issues. Flow chemistry offers a more streamlined and continuous synthesis process as well as a variety of advantages compared to a batch operation. Incorporating a flow operation results in increased production with decreased capital. In terms of safety, flow reactors for pharmaceutical reactions are normally run in much smaller volumes than those of batch reactions. Dealing with toxic chemicals is also safer – cytotoxic APIs can be produced in inexpensive, dedicated, and disposable equipment sets for production of low volumes of these compounds in the laboratory fumehood.

Not only is flow chemistry safer than batch, it is also more efficient – better heat and mass transfer alongside less back mixing contribute to enhancing the purity profile and product recovery. The small size of the microreactors, either PFR or CSTR, allows for much higher reaction temperatures and pressures as compared to batch reactors, enabling us to safely perform reactions that were previously unstable in batch. Reactions can also undergo superheating, enabling them to be heated above their boiling point, further resulting in faster reaction rates. The flow operation reduces the break time between consecutive steps and can significantly reduce the manufacturing time.

An important advantage of flow chemistry is the ability to fully control many of the parameters, such as mixing, temperature, and reaction time. By having the capability to add or remove heat almost instantaneously, one could remove the heat generated from a reaction; for exothermic reactions or a reaction requiring hazardous materials, this is an especially important benefit. Flow reactors also allow control over residence time, which is the time that the reaction is exposed to a set temperature, allowing for far more precise reaction times. This is immensely beneficial, particularly if a reaction creates more than one product. There is also continuous monitoring of the quality – such as purity – by online or offline sensors, so parameters can still be fine-tuned during the operation in order to obtain the best product quality. During a batch process, you would need to wait until reaction is completed, and by then it may be too late to make any adjustment.

The intense mixing in flow chemistry is provided by microreactors, which enables scientists to use multiple phase systems and fewer solvents, and produce purer material – reducing unit operation and work-up steps. The high temperature-high pressure flow reactors reduce reaction time and provide better conversion whilst using starting material more efficiently. This requires tightly controlled process analytical technologies (PAT), and resolution of any quality assurance issues related to acceptability of the intermediates. Microreactors can be designed to fit the requirements needed for the reaction, therefore providing customisation opportunities. In addition, microreactors have low maintenance and operational costs without abandoning productivity and efficiency, which provides an economic incentive. These technological advancements are valuable and vital assets in flow chemistry and have expanded the versatility in its use.

Although the advantages are clear, before a flow process can be developed, a working small-scale batch process should still exist since, in general, developing a flow step may take much longer than its batch equivalent. However, once a flow step has been developed, its scale-up is far easier and encounters fewer issues than in batch. The reason for this is that the sizes of the reactors in the scale-up version are normally less than 20 times the lab version. For example, the diameter of lab-scale PFR tubing is normally around 1/16" - 1/4", and its pilot plant version is around 3/8" - 1/2" – these are not very different in size. The scale-up in the batch process could be 100 to 1000 times bigger than the original lab-scale process – this is impractical as mixing and other engineering aspects can complicate such large scale-up operations.

The flexibility and versatility that continuous flow allows cannot be disregarded – minimal adjustments are needed in a flow operation to increase the capacity of the reactor. For example, scaling up, numbering up, or scaling out, which is increasing the capacity of microreactors, increasing

the amount of micoreactors, and running the reaction for longer, respectively. There are four types of flow systems which have distinct features, specialised for different reactions. Type 1 and 2 are for catalyst-free reactions, where type 1 has reagents flow directly through the microreactor and type 2 has a reagent in solid state. Type 3 and 4 require a catalyst, whereas type 3 has a homogeneous catalyst flowing through the system, and type 4 has the catalyst confined to the reactor as the reagents flow through, making it useful for multistep synthesis.

The total cost of producing a final product depends on the cost of the process R&D, starting materials, and the operational costs – of these, the latter two have the greatest impact on the overall cost. Using the flow operation, cost incentives include the reduction of energy costs and reduction of impurities and waste products. Awareness by chemists of the capabilities of flow chemistry as an enabling technology gives them the power to design shorter synthetic routes, and therefore also reduce the cost once operational. Of course, reducing waste promotes efficiency, enhances purity, and is beneficial to the environment. Companies may realise too late that their drug has an excessive, multi-step process that could have been shortened and since their cost would be unnecessarily high due to a longer synthetic route, this could result in losing substantial amounts of profit.

If we assume that flow facilities provide major benefits at larger scales, we could see that later-phase and commercial products are more amenable to continuous processing. Big pharma such as Lilly, GSK, and Novartis are already preparing for launch of their pilot or commercial plant facilities and, at this time, these plants are built within their own companies. However over time these companies may decide to outsource such operations to CMOs or CDMOs – we have one such flow chemistry partnership with big pharma, but we're very much in the minority. Our belief is that it's only a matter of time until much more flow work is outsourced, and we have kept part of our capacity free in anticipation of this.

During development, flow steps seem to be more appropriate for early steps of the synthetic route where less expensive raw materials are available for process development and the volume of the material to be processed is more. Perhaps the majority of the APIs currently produced at a commercial stage have the required volume to be turned into flow. However, due to regulatory issues, limited changes can be applied to the existing commercial processes but it can still potentially be achieved with some investment and time.

The transition from batch to flow operation is generally thought of as both costly and inconvenient, but implementing this change in early development is simple and beneficial. Comparing Phase I and Phase III, it is much easier to manage changes in development and regulation if switched at Phase I, but to switch at Phase III would result in a delay in market release and a loss in both time and money.

Yet, the number of flow steps during development remains stubbornly below 5%. The message here is clear: for flow chemistry to deliver on its huge promise, pharma and CDMOs need to build the platform into the Phase I process R&D of innovative API programmes. This requires commitment from the beginning of a project, and a wider commitment to running in flow whenever possible. Flow chemistry has suffered slow implementation into the industry – especially as compared to some other industries such as oil and gas – even though more are beginning to recognise its benefits. This is largely due to the increase in demand for flow chemists while there remains a lack of experience and education in the field. With an entirely new manufacturing process, people may be reluctant to adopt it as they think it may slow down the manufacturing process, something which the FDA may be able to combat through deregulation. The safety, efficiency, and flexibility of flow chemistry are what drives its high interest, and are why it's becoming an essential component in research, development, and for the future of the industry.

This article has been abridged from STA Pharmaceutical's contribution to the CPhI Annual Report. **http://www.cphi.com/europe/cphi-annual-report**

Dr. Sam Tadayon

is a Chemical Engineer, PhD, with research focusing on Process Engineering in Pharmaceutical Industry. He worked in Wyeth Pharmaceutics for around 8 years before joining STA Pharmaceuticals in Shanghai/China in 2011. Since then he is leading the Process Engineering team of around 40 scientists including the flow chemistry team. Dr. Tadayon has been involved with around 400 projects mainly involved with process development of crystallization, flow chemistry, and other chemical engineering aspects of the pharmaceutical processes.

Email: sam_tadayon@wuxiapptec.com