Manufacturing in the 21st Century: Continuous Flow Chemistry has Arrived

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Submitted: 09/15/2014
Accepted for Publication: 09/24/2014

Introduction

If you entered a modern factory, it would look a lot like a factory of the 20th century. In fact, the basic design of a stirred tank reactor has changed little over the last one hundred years. Today, things are really starting to change. In the future, manufacturing trains may look more like a Rube Goldberg device that the factory of the 20th century.

Continuous Flow Technology: Disruptive Innovation

Dr. Clayton Christensen, professor at Harvard University, coined the term *Disruptive Innovation* which "describes a process by which a product or service takes root initially in simple applications at the bottom of a market and then relentlessly moves up market, eventually displacing established competitors."[1] This is what we have seen in the use and application of continuous flow technology. In addition, advances have pushed the technologies to the forefront making them easier to use, broader in scope of application, and economically acceptable.

This could easily define the path of continuous flow chemistry in the pharmaceutical industry. Often these technologies were designed to produce the initial quantities of new pharmaceuticals in order to do animal studies or to gather early toxicology data. The idea of allowing the reactor to run overnight to produce the desired quantities was normal. How many chemists ended their day checking the connections on the water batches or making sure the flow rates on an HPLC column were tight?

These micro reactors, already used in other industries, eventually gave way to better designs and higher throughputs. Those HPLC units were eventually replaced by Simulated Moving Bed (SMB) Chromatography units. Before you know it, 10's of output grams became kilos and then kilos became tons. Today, these technologies are replacing standard stir tank reactors and changing the footprint of our manufacturing plants. Continuous Flow Technologies have arrived. The risk-averse

pharmaceutical industry started to recognize the advantages of these new technologies.

Continuous flow technology is a broad-based term that encompasses different type of technologies. At times, we interchange a wide range of terms to describe the art and the applications. To start, we often talk about continuous flow processes when we actually are describing a single chemical step in a long process. This point is going to be more important later in this discussion. While flow chemistry is good, it is not the best solution for all chemical reactions and sometimes batch vessels are just as good giving the same or better results.

A Brief History of Continuous Flow

One of the oldest continuous operations is Simulated Moving Bed Chromatography (SMB). The basis of the technology can be found in early patents dating back to the 1950's. By the late 1990's, it was being used to produce a wide range of pharmaceutical intermediates and eventually Active Pharmaceutical Ingredients (APIs). As with many emerging technologies, it was originally considered to be too expensive for practical use. Often it was even considered by chemical development people to be a failure. If the development group members saw chromatography in the process, their first idea was to remove it. This has changed considerably over the years and when the process is viewed in its entirety, the reduced levels of solvents, higher purities, lower operating cost, and reduced development time yield a more efficient and cost competitive approach.

The initial point of entry for commercial application is high. However, the applications continue to grow, and the efficiencies of the equipment and the overall robustness of the processes are very high. A critical part of any chromatography process is the stationary phase. The industry continues to develop newer and better stationary phases. This allows the overall costs to drop considerably. In addition, the stability of the stationary phases has also increased dramatically over the year allowing for not only a broader range of separations but a more stable overall process with less down time. Lower cost Stationary phases that are more stable and more efficient are a significant driver in the adaptation of SMB applications in a commercial setting.

Work has also been done developing more efficient equipment. The adoption of new controls has allowed increases in production from existing equipment to climb by 20% or more.[2] As with any process, the more output per unit, the lower the cost.

Broader Efficiencies

The process improvements do not stop just with the chemical separation. The downstream processes also make a significant difference to the overall cost. SMB units operate some type of continuous evaporation and solvent recycling. Recovery of solvents has ranged in the high 90%. UCB Pharma has published results in the past demonstrating the solvent recovery to exceed 99%.[3] This allows not only for a reduction in costs but also greener processes.

Today, several drugs have been reported to use SMB for their manufacturing. In addition, SMB processes are not limited to just large volume products. Several companies have reported that they have used smaller SMB units to produce high potency drugs. Consider that these are closed systems and the stationary phase, while not a single use item, is dedicated to only one product.

In today's market, time is often critical. SMB process with new computer modeling systems can be developed rapidly and scaled up in relatively short time. Larger amounts of material required for clinical trials can be rapidly produced. This would allow the clinical trials to proceed and can contribute to valuable time saved in the development of a new drug.

Another important aspect of SMB processes is that they can be added on to other continuous processes. Downstream processing can continue without any distribution, and in-line mixing can readily adjust solvent concentrations to fit the SMB units.

SMB: A Regulatory Perspective

From a regulatory point of view, the FDA has already had the opportunity to review the manufacturing processes for several drugs in which the SMB process has been a critical step and important for the manufacturing of a new APIs.

Continuous processing continues to evolve and find increased acceptance and applications in the manufacturing of APIs. As the idea moved from the lab to the pilot and eventually into production, the pharmaceutical industry has been one of the slowest groups to adopt this technology. Today, they are beginning to find that it is a real game changer and continue to add more applications to the tool box. Years ago, when the FDA issued its guidelines on PAT, one Big Pharma firm commented that continuous manufacturing would be inefficient.[4] This was, for many years, the general conception of continuous chemistry.

Eroding Barriers to Adoption

We are aware of the basic advantages to the use of continuous flow technology. In general, the chemical industry has used the technology to handle explosive and dangerous chemistry. It has been well documented in the applications such as nitration reactions. However, there has been a reluctance from the overall industry to adopt the technology.

There have been some good reasons for this, but many are going away. To begin with, there is an overall abundance of chemical capacity in our industry and the idea of investing in more is not an easy sell for most of us. This is also an industry in which people would rather follow instead of lead. Considering most of our drugs are coming from the small emerging companies, these companies are more concerned with getting product and getting to Phase II. By then, they often have a partner who will be responsible for the manufacturing. Also consider that most drugs never make it to market so investing in some of these is not always easy.

The result is that the Contract Manufactures Organizations (CMOs) have had to adapt to this dynamic. Many of these companies have developed relationships with equipment manufacturers, or they have partnered with universities or technical centers that specialize in flow chemistry. This can reduce the risk for the CMO while giving them the time to develop new technologies.

In the end, the real sell for the technology will be in the cost savings. As energy costs continue to rise, these smaller reactors can easily reduce energy cost by over 20%.[5] In addition, there are many cases reported where the use of flow chemistry can reduce the impurities and therefore significantly reduce the waste solvents. For High Potency Drugs (HPAPIs) this can be a considerable cost incentive.

With the smaller reactors, the investment in new equipment can be reduced as well. The lower Capital Expenditure leads to lower costs and a better chance for investments. Couple this with the ability to run many hazardous reactions safer, and it would seem that using these new technologies would be strongly favored in the end.

Impact on Business

It is not just the chemistry that is changing; the business end of the process is also going to change. With the use of flow chemistry, we are looking at more dedicated manufacturing lines and fewer multi-purpose chemical lines. It is conceivable that eventually every product will have a dedicated manufacturing train, regardless of the volume of drug produced. The age of the multi-purpose plants could become a thing of the past.

This could fit well with the future of the drug industry and the development of more potent drugs in general. In principle, the volumes are going down and personalize medicine may force us to be more flexible and produce even small volumes of products in the future.

Continued Advances

There have been papers written demonstrating the advantage of flow chemistry. It is hard today to pick up any scholarly journal covering chemistry without articles describing flow chemistry. We continue to find new ways to adapt the technology.

Consider some of the advances in fixed bed catalytic transformations or tethered enzymes and ligands. These have led to more efficient transformations and reductions in cost.

Still today, we are looking at a combination of batch and continuous flow chemistry in the same process. However, more chemists are looking at pairing more than one chemical step. Combinations of chemical reactions followed by SMB purification/separation is being looked at today. The elimination of additional drying steps, as well as overall solvent reduction, is just part of the attraction.

More Than Small Molecules

If you think, *"It is just the manufacturing of small molecules,"* think again. The production of biologicals has long been using Chromatography or their purification and polishing steps. Companies are developing new reactor designs to be used with the biologicals in general. This will complement the single use technology very well. Who would have thought that stainless steel vessels would ever be considered to be single use equipment? Such is the case today.

There are multiple areas where bioprocessing could be adapted to continuous processing. Continuous processing has already led to reduced reactions times. Issues around scale-up can be minimized like in chemical synthesis. In process development, the same unit that ran well for several hours can be used to run for several weeks or months. In addition, reactor conditions that were not considered in the past can be viable alternates for the manufacturing processing. The same advantages that we see in operating continuously in the chemical synthesis can be seen in biological transformations.[5]

An Unlikely Leader

For this to continue to grow, you still need a champion. Either someone or some group needs to go forth and lead the way preaching the message. Who would ever think that one of the champions would be the FDA? In 2011, Janet Woodcock, Director of the Center for Drug Evaluation and Research, stated, "Right now manufacturing experts from the 1950's would easily recognize processes today. In 25 years, these same processes will be obsolete." In 2012, Sharmista Chatterjee, CMC Lead for QbD ONDQA/CDER spoke at the IFPAC Annual Meeting and made it clear that there was nothing in the regulations that prohibit one from going continuous. Dr Chatterjee, in the summary of the talk, was clear that the "Science exists to enable continuous manufacturing of pharmaceuticals."[6] Christine Moore, Deputy Director for Science and Policy INDQA/CDER, spoke later and delivered a similar message.[7]

Our concept of what a batch is will change dramatically in the future. The idea of measuring the batch size in terms of days, weeks, or months sounds far out, but no one expected to produce tons of material in units that are the size of a typical office desk or operate chemistry at very high pressures and temperatures. I can only imagine producing for 12 months which would result in the formation of only one batch.

Beyond APIs

The story does not end here however. Continuous operations are not limited to just the manufacturing of the API's. We have already seen manufacturing plants implement continuous granulation technologies as well as drying for the manufacturing of solid dosages. Anyone who has seen tablets and capsules produced would have to agree: as long as you continue to feed these units, they will produce a product. Many of the unit operations for dosage manufacturing can be done continuously.

Dr. James Evans of Novartis-MIT discussed in 2010 at AAPS's annual meeting the potential concept of synthesis through tableting and bottling. It has been reported that at MIT, they constructed a small unit that starting from basic raw materials to API, finalizing in actual drug in a bottle. This is not the first time this has been considered, and the idea of a single unit producing both the API as well as the dosage in a single manufacturing line could eventually be the next *Disruptive Innovation*. Dr. James Kraunsoe of Astra Zeneca spoke about the work they were doing in continuous granulation and how many processes are inherently continuous. He stated, "These opportunities need to be appreciated, evaluated, collaborated on, understood, and pursued."[8]

Conclusion

In summary, many of the reasons not to go continuous have been eliminated, and the industry and the regulatory authorities have now recognized the importance and value of continuous processing. For the process development team—whether it be synthesis, bio-processing, or formulation—they have opened the tool box and found a new set of tools to play with. For the regulatory agencies, they have recognized the economic, environmental, and safety values that going continuous can benefit the health care system. We are only left with what could be the hardest part of the program: getting the business unit to recognize that the investment will bring greater value in the future.

References:

1. Christensen C. Key Concepts. Disruptive Innovation page. Available at: http://www.claytonchristensen.com/key-concepts/#sthash.mob8SN1K.dpuf. Accessed September 19, 2014.
2. Hombourge, L. Application of the Varicol process to the separation of the isomers of the SB-553261 racemate. *Journal of Chromatorgraphy*.2002;947:59-68.
3. McCormick, D. In the loop: Continuous Chromatography for Chiral (and other) Separations. *Pharmaceutical Technology*. 2006;30(5):54-59.
4. Afrnan A. Continuous Manufacturing in Pharma: Myths and Missed Opportunities. *Pharma QbD*. Updated May 3, 2011. Available at: http://www.pharmaqbd.com/continuous_manufacturing_myths_afnan/. Accessed September 19, 2014.
5. Whitford WG. Supporting Continuous Processing with Advanced Single-Use Technologies. *Bio Process International*. Updated April 1, 2013. Available at: http://www.bioprocessintl.com/manufacturing/antibody-non-antibody/supporting-continuous-processing-with-advanced-single-use-technologies-341766/. Accessed September 19, 2014.
6. Chatterjee S. *FDA Perspective on Continuous Manufacturing*. Presented at the IFPAC Annual Meeting: Baltimore, MD. 2012.
7. Moore C. *Continuous Manufacturing-FDA Perspective on Submissions and Implementation*. Presented at the 3rd Symposium on Continuous Flow Reactor Technology for Industrial Applications: Lake Como, Italy. 2011.
8. Thomas P. Continuous Granulation at AZ: Where It Fits in Tablet Manufacture. . Updated November 23, 2010. Available at: http://www.pharmaqbd.com/continuous_granulation_astrazeneca_kraunsoe/. Accessed September 19, 2014.

Author Biography

James Bruno *has over 40 years of industrial experience manufacturing APIs. He has been consulting for over 10 years servicing the merging pharma companies focused on manufacturing APIs in a regulated environment, including the technical and regulatory aspects of the product. More strategically, Jim helps CMOs to focus their work and review their assets to function in these markets globally. In order to expedite the production of new compounds, Jim also works to bring technologies like continuous flow chemistry including chromatography as well as catalyst and membrane technology to solve chemical problems. Jim is a DCAT Past President and Scientific Advisory Board Chairman at Rider University.*