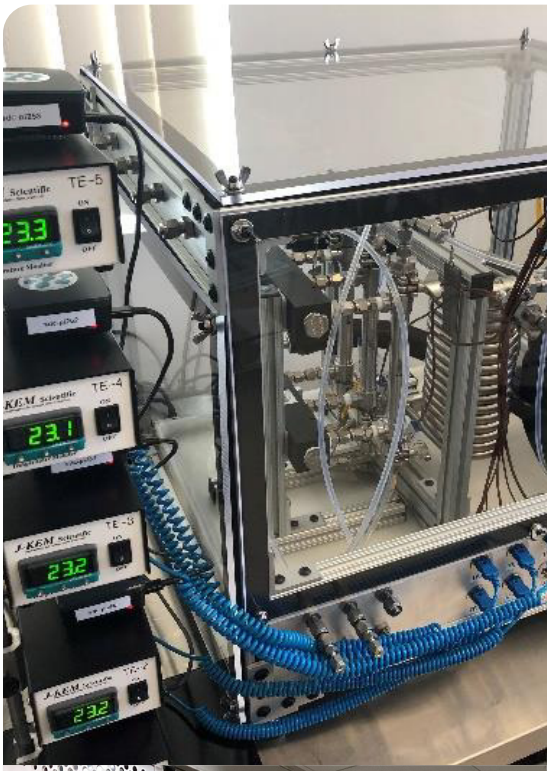
Continuous manufacturing: An evolving technology for drug substance manufacturing



Continuous chemical manufacturing technology has been in use for more than 100 years producing high-volume commodity chemicals. However, it was not until the early 2000s that the technology caught the attention of the pharmaceutical industry in a significant way.

A noteworthy milestone was in 2007, when a grant from Novartis to MIT led to the creation of the Novartis-MIT Center for Continuous Manufacturing, an ambitious multi-investigator program to integrate continuous drug substance and drug product manufacturing.[1] There are several reasons why the adoption of continuous manufacturing (CM) for drugs lagged applications elsewhere. The broad diversity of chemistries used to manufacture drugs and the multitude of unit operations make the general application of CM complex. Additionally, the relatively small annual production volumes of individual drug substances do not benefit from the economies of scale provided by CM, when compared to large volume commodity chemicals. For pharmaceuticals, the motivating factors likely include the desire for greater quality control, along with expected improvements in safety and efficiency. The Novartis-MIT project culminated in a 2013 publication describing an end-to-end continuous process to produce aliskiren drug substance, and formulated drug product, at pilot scale.[2]

Following up on this initial effort, in 2014, the 1st International Symposium on Continuous Manufacturing of Pharmaceuticals was held in Cambridge, MA. The meeting resulted in a series of aspirational white papers envisioning the future of CM technology.[3] Also in 2014, the FDA Center for Drug Evaluation and Research (CDER) established its Emerging Technology Program to promote and facilitate industry adoptions of innovative technologies with CM as a major focus. The vision was clear: end-to-end CM would replace batch processing as the preferred method of manufacturing new drug substances, resulting in dramatic improvements in quality control and greatly reducing cost via small footprint manufacturing facilities.

Today, CM is an essential tool of drug substance manufacturing, although not necessarily in the way envisioned during those early days. CM is typically part of a hybrid approach to drug substance manufacture, used side-by-side with batch processing to overcome technical challenges for individual reactions and unit operations. The use cases for flow are often the result of increasing complexity of investigation drug substances. As new synthetic methodologies such as directed arene metalation and photochemistry became available, discovery chemists have used these technologies to develop densely functionalized clinical candidates that are difficult to manufacture by other

means. Molecular complexity is also driving the use of new and diverse synthetic technologies, some of which require reactive and hazardous reagents that are difficult to manage safely, or are functionally incompatible with batch technology. Herein we highlight some particularly fruitful applications of CM at Cambrex and Snapdragon as an enabling technology for drug substance manufacturing.

Organometallic reactions

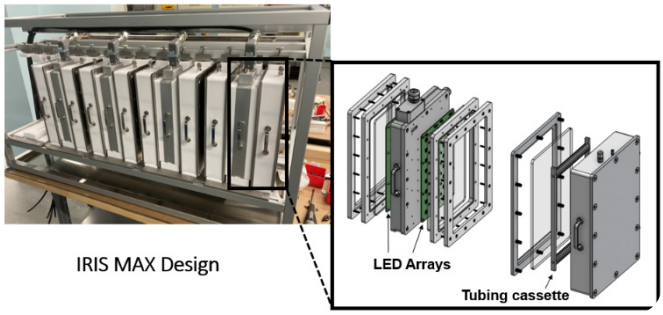
One of the major applications of CM has been manufacturing via unstable organometallic intermediates. Directed ortho metalation technology has proven an essential tool for preparation of functionalized arenes such as the boronate components in widely used cross-coupling reactions. The selective formation and reaction of organometallic reactants typically requires cryogenic reaction conditions to manage exotherm and the instability of the products formed. Flow processing renders these reactions practical through precise control over the mixing, efficient removal of heat, and rapid utilization of what is often a short-lived species.[4,5]

In an example from our labs, an unsymmetric ketone was assembled in a highly efficient manner by sequential addition of an alkyl Grignard and lithiated pyridine to a carbamoyl chloride. In flow, the instability of intermediates in the process was effectively managed through tight control over both temperature and residence time prior to quench in a flow system.[6] The ability to continuously control the stoichiometry of reactants introduced to a fast-mixing plug flow reactor simplified the meta-halogen exchange of 2,6-dibromopyridine to selectively deliver only the desired monolithiated species in high yield.

The ability to operate under pressure in liquid-filled tubular reactors with efficient mixing simplifies the use of gaseous reactants providing for efficient and safe use of such reagents. This technology has been invaluable in our labs. In a published example, we demonstrated the selective lithiation of allene gas which was then engaged in an asymmetric, zinc-mediated addition to an aldehyde to deliver a diastereometrically enriched propargylic amino alcohol, avoiding a multistep alternative route and delivering the product with good atom efficiency.[7]

Unstable reagents

On the small scale typically employed in the medicinal chemistry lab, energetic, hazardous, and even unstable reagents can often be used effectively to readily access



complex structures. When these projects advance as candidates for clinical study, the avoidance of these reagents may necessitate complete redesign of the synthetic route. The resulting route scouting and process design activities can lead to significant delay in accessing bulk drug substance required for tox and clinical studies. Continuous manufacturing can obviate the need to develop an alternative synthetic route by enabling safe scale-up, even with reagents that would be prohibitively hazardous to handle on scale. Phosgene is a stable, albeit highly toxic, reagent typically avoided in pharmaceutical manufacturing, yet it is such an important industrial chemical that dedicated continuous generators are commercially available.[8] Unstable reagents are more challenging, requiring carefully choreographed preparation and utilization. Continuous generation connected to continuous or semi-batch utilization is a pathway to scaling processes with these agents.[9]

We have demonstrated a practical and scalable continuous reactor system to generate diazomethane — a useful gaseous reagent that is both highly toxic and thermally unstable. To separate diazomethane from the byproducts of its formation, we extracted the diazomethane into the gas phase from the crude preparation reaction with nitrogen. The nitrogen stream of diazomethane, at concentrations safely below the lower explosion limit, was then redissolving liquid solvent as a pure reaction ready for downstream reaction.[10] This technology provided ready access to bulk quantities of a challenging cyclopropane structure without need to redesign the route.

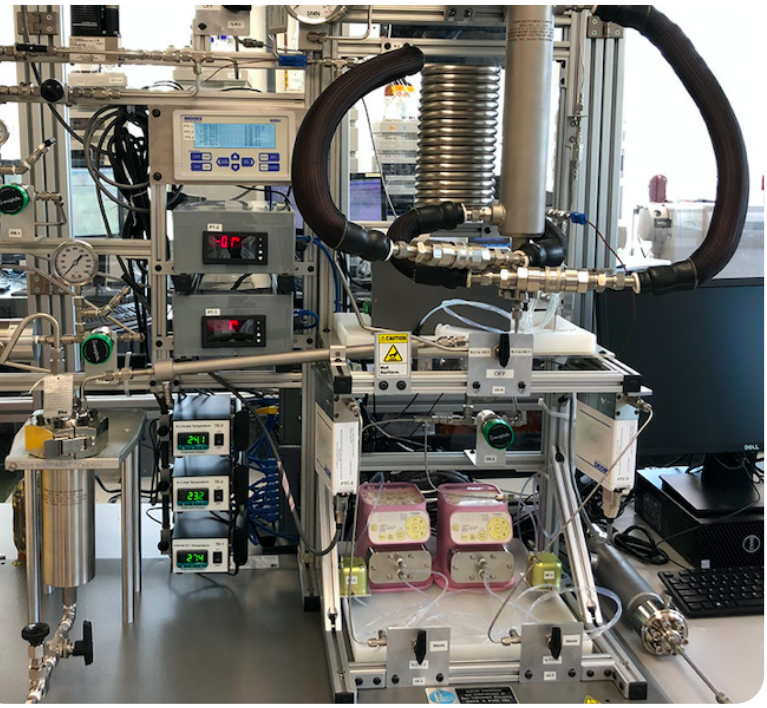
High-temperature reactions

Tubular reactors can be designed with large heat exchanging surface area relative to batch reactors. Tubular reactors can also accommodate much higher operating pressures than are typically available in batch, and certainly at much lower cost than a comparably

rated batch reactor. That combination of highly efficient heat transfer and the ability to operate at high pressure allows for practical application of high-temperature, short-duration reactions in process-friendly solvents. This technology can be useful in overcoming the high energies of activation characteristic of transformations such as Cope and other skeletal rearrangements. In a recent example, the desired atropisomer of a late-stage intermediate was obtained via classical resolution leaving behind large quantities of the undesired isomer, which could be racemized by heating to >300°C for a few minutes; conditions which resulted in a reaction pressure in excess of 30 bar. Despite the extreme conditions, we successfully developed a scalable continuous process using a tube-in-tube, oil-heated reactor. The racemate could then be resubjected to resolution providing much improved E-factor and greater quantities of the target drug substance.[11]

Photochemistry

Photochemistry has enjoyed renewed interest from the synthetic community over the last 20 years. Numerous new photochemical methodologies have been developed affording unique functional group transformations and efficient bond formations difficult to achieve in other ways. Consequently, photochemistry has become a standard tool in medicinal chemistry labs.



The advancement of clinical candidates constructed using photochemistry has motivated the development of scalable photochemical processes and equipment.[12] Photochemistry development is complex in that the design of the photoreactor has a significant impacton the process performance, as reactor design dictates both the stoichiometry and concentration of photons delivered. As a result of Beer-Lamber Law, efficient photoreactors, particularly where the quantum yield for the reaction is less than one, are designed to irradiate thin films of the process stream. Our photoreactor system is designed around irradiation of transparent and disposable polymer tubing encased in a housing that allows for precise temperature control of the process stream. We have designed a photochemical platform that maintains similar photophysics from a 100W lab development reactor through to a multikilowatt production system designed for GMP applications. By maintaining a common design in both the lab and production reactors, we can predict scaleup performances and move rapidly from proof-of-concept to production.

Membrane technologies

Membrane separation techniques such as tangential flow filtration (TFF), nanofiltration and pervaporation are established manufacturing technologies used to separate molecules based on molecular size. As flow systems by design, these separation technologies can be readily applied to drug manufacturing. We have utilized TFF technology for the purification of synthetic polymers and nanofiltration for solvent exchange. Pervaporation is less commonly applied to pharmaceutical production, but widely used in the petroleum industry. A notable application of pervaporation is the removal of water from esterase-catalyzed esterification to drive equilibrium toward product.[13]

Inspired by this example, we examined the application of pervaporation to the problem of ring-closing metathesis reactions. Typical substrates for this reaction result in the formation of ethylene as by-product. Ethylene present in the system not only leads to reforming starting material due to equilibrium, but also contributes to catalyst decomposition. Ethylene removal in batch processes has been accomplished by sparging a batch reactor with nitrogen or running the process under vacuum. Both techniques are challenging to operate safely, difficult to scale, and incompatible with volatile substrates and/or products. We have now demonstrated that pervaporation can be used to selectively remove ethylene and drive ring closing metathesis equilibrium

toward product.[14] The process can be fully characterized on small scale in the lab using flat sheet membranes and then accurately scaled by orders of magnitude to hollow fiber membrane configurations using well established scaling factors.

Conclusion

In the nearly two decades since initiation of the Novartis-MIT collaboration, the application of CM technology for pharmaceuticals has gone from aspirational to reality.

Today, it is common to apply CM to enable technically challenging reactions and unit operations in drug substance manufacturing. However, it is more likely to be found integrated with upstream and downstream batch processing, resulting in an overall hybrid manufacturing process. Adoption of CM technology will continue to grow and evolve as the complexity of synthetic drug substances continues to increase and methodologies such as photochemistry and electrochemistry are used to discover new clinical candidates.

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