

# Continuous manufacturing of drug substance and small molecules: process and equipment view

**KEYWORDS:** Continuous manufacturing, drug substance, process design, process intensification, flow chemistry, continuous crystallization.

## ABSTRACT

The continuous manufacturing of pharmaceutical compounds and fine chemicals is in high interest for the industry due to significant technical, quality, and economical advantages. This manufacturing method has its own challenges. Beside the more efficient, safer, and greener synthesis route, a new process design paradigm and equipment selection and design is required. Defining system dynamic to correlate critical quality attribute of final product to critical process parameters is crucial for ensuring consistent product quality and process robustness. This work will provide a high-level overall view on the advantages and challenges of continuous manufacturing and review the process and equipment design considerations.

## INTRODUCTION

The continuous manufacturing (CM) of pharmaceutical compounds and fine chemicals is well practiced in the industry. However, the maturity of the technology and implementation of the technology is not uniform across the board. Some developed techniques and industrial applications go back to early 1900s, extensively in petrochemical and fertilizer industry. The Pharmaceutical industry has started adopting the technology in the recent decades, at different scales and applications. The overall concept of "Continuous Pharmaceutical Manufacturing" has been treated unfairly by industry and regulators, since the investors, regulators, and managers have used a single measure for the entire pharma industry. The bio/pharma manufacturing processes can be categorized into four sections, Small Molecule Drug Substance (DS) or active pharmaceutical ingredients (APIs), Small Molecule Drug Product (DP), Upstream Bioprocessing, and Downstream Bioprocessing. Hence, each section has its own nature, workflow, challenges, sensitivity (technical, quality, regulatory, and financial), and potentiality for CM. Most of the regulatory scrutiny is on the DP for safety, content uniformity, process robustness and stability. The API side is relatively more "relaxed" on the regulatory scrutiny, has more opportunity for process intensification and novel methods for CM, and also more potentiality for return on investment for CM and process intensification. Therefore, there have been more efforts and successful implementations of CM in the API lines in manufacturing scale. However, this "low hanging fruit" comes with its own benefits and challenges, which span from technical to economical battles.

This paper focuses on CM processes and equipment for API with a high-level overview of the particular considerations for process robustness and reliability for prolonged utilization in continuous fashion. Interested readers are referred to numerous publications on each topic, which some are cited here.

## CONTINUOUS MANUFACTURING PROCESS OF DRUG SUBSTANCE

### Benefits and Challenges

The main benefits of CM of APIs can be summarized in four main categories:

- Process intensification for reduced footprint and energy/resources utilization to reduce manufacturing cost (Capex vs Opex).
- Higher throughput over long production time and improving logistics planning
- More consistent product quality and easier automated control
- Enabling platform for new synthesis routes and green chemistry and safety

The process scale-up is more attainable in compare to batch, and the modularity nature of the process equipment can bring significant flexibility in process changes and time for execution and new process/location development. The smaller footprint requires less GMP utility and cost and smaller skids, which don't need extensive foundation preparation and buildings. Moreover, reactions involving hazardous gases or explosive intermediates, when run in large volume and cumulated amounts, pose a safety issue. In CM, due to the smaller dimensions and small cumulation, the process become safer and greener.

The main challenges for the paradigm shift from batch to continuous processes can be categorized into four categories:

- Asset utilization (in compare to the existing batch equipment) and new investment justification
- Cultural issues in organization, training for operators, and entrenchment of batch operation practice
- Regulatory concerns for change of process
- Demand and logistic for short-term needs and "small batch" purchases

The pharmaceutical industry has traditionally preferred batch processing largely because of GMP documentation and

traceability purposes, although the chemical engineering knowledge of CM process and equipment has been prevailed. For many API manufacturers the expensive batch scale equipment is paid off over years and the ROI analysis for new Capex doesn't make sense. This reinvestment burden extends to regulatory certificates, customers approved process, training operators, operation cost, and lack of process rejuvenation appetite that convince them to keep the status quo, especially when the profit margin is large enough that covers inefficiencies in the manufacturing process. A few major large pharma companies are already invested in the CM (such as GSK and Eli Lilly). However, the adaptation has been more pronounced in generics, CMOs, and fine chemical companies, mostly due to the manufacturing cost saving, which is relatively a significant portion of total cost.

### Brief Overview of Chemistry

There are more than a hundred new synthesis routes and CM processes for APIs explored and reported by academia and R&D labs (1, 2). The scales are from microfluidics to kilo-scale and at diverse chemistry and phases. Interested readers can refer to numerous publications and books in this area. There are also several commercial scale CM lines for APIs, such as GSK's Fluticasone, Eli Lilly's bicyclic isoxazolidines, Novartis' Aliskiren, Sanofi's Artemisinin, BMS' Hydroxypyrrrolotriazine, Eli Lilly's prexasertib, and few more. These processes are in different scales and are combination of End-to-End or hybrid batch-continuous.

For many of the mentioned CM processes a new synthesis route has been developed, by new solvents, process conditions, reduced steps, new catalysts, new equipment, or new activation methods such as photochemistry. Although the reactions are designed to be efficient with high selectivity, some new impurities could be formed from side reactions that are being studied in the new impurity fate map. Also new risk assessments to identify the quality attributes (CQA) and process parameters (CPP) effects have been performed. The CQAs for final API are similar to the batch process, mostly on impurity level, particle size distribution, polymorph content and stability. The key objective for the new flow-chemistry process is to produce same APIs at lower overall cost, safer process, more efficient process and easier to run/control, shorter time, few steps, greener, and with more consistent quality.

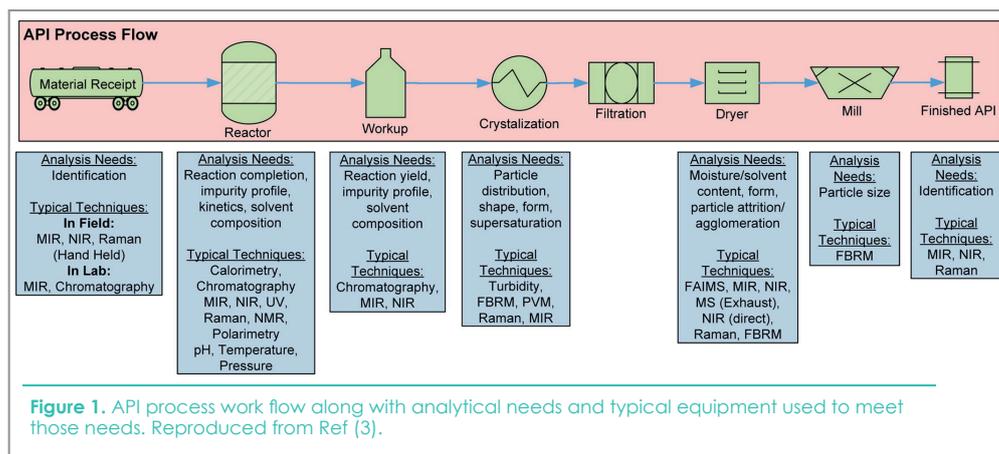
### Continuous Process

It was mentioned before that the CM can be a hybrid mode of some batch steps and some continuous or end-to-end continuous. The process starts with incoming raw material from supply chain (or being produced on site), synthesis of crude API, and purification and final form preparation (Figure 1).

Due to GMP requirement or process needs, there are several types of information need to be generated, monitored, and recorded. Figure 1 provides an over view of the API process work flow along with analytical needs and typical equipment used to meet those needs. PAT tools, control systems (SCADA), some surge vessels, and deviation valves also will be used along the process. The CM components work in tandem in a harmonized fashion (material flow and data flow) without

interruption. The telescopic and connectivity of the process creates two major differentiating concepts with batch here:

1. Residence Time Distribution (RTD): This is an important measure for any disturbance in the system, control strategy, and start-up and steady state operation. Although the material flow could pass process/material disturbances, the rate and pattern are not an ideal plug flow curve, especially for the CSTRs in the system. The overall RTD also is separated to individual equipment RTD and process RTD. There is also a possibility to define interim RTD, for instance, for synthesis section (including several reactors and separators). The RTD shows how the system responds to any duration and magnitude of material/process disturbance. For example, if one of the reagents pump trips for 10 seconds and flowrate of that reagent ramps down to 80% (disturbance of 20% for 10 second) then: A) what would be effect on distribution of impurity over time (or other unreacted reagent), B) how long it would take to notice the effect in downstream, and C) how long it would take to regain the steady condition after the disturbance resolves (by operator intervention, or control system).
2. Upstream effect: As described above the process connectivity required continuous flow of material from start of the process to the downstream steps. Any changes in upstream, in inlet material, or at process parameters, would change the entering materials to the consecutive steps. The changes can be in flowrate of materials, for example for the pump failure case, or product/by-product ratio, for example due to temperature change in reactor (heater/cooler failure). The utilization of surge drums and deviation valves become very important here to interrupt the flow and maintain the quality and flow of materials trickling to the downstream steps. The surge drums and deviation valves location and decision on volume and activation mode comes from process modelling or experimental evaluation and will be defined in the design stage. Some mitigation plans also could be necessary to protect equipment. For instance, if a process disruption could cause solid formation in the line and the solid content could precipitate and blocks the transfer line, then solvent injection will be required to flush the line before the process collapses.



### Process Design

Considerations for the continuous process design for API manufacturing are similar to any other process industries. Starting from market research and demand evaluation for defining the scale or throughput, equipment sizing based on scale and multiphysics for micro-mixing, reactions yield, and required residence time, safety and process control requirements, design space identification, and

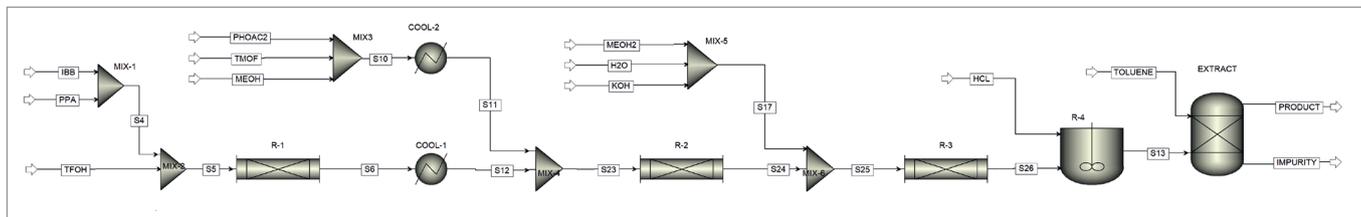


Figure 2. Steady state process simulation for continuous manufacturing of Ibuprofen from ref (5).

technoeconomical analysis for Capex and Opex, which yields to process optimization.

Via the transport phenomena intensification and utilization of extremified reaction activation tools (such as higher temperature or pressure) reactions can perform at faster reaction rate. High pressure increases the rate of reactions with negative activation volume and also suppress boiling point of the reagents. Therefore, superheated reactions can be achieved at faster rate. Small reactors offer a great platform to maintain isothermal conditions throughout the operation and minimize the formation of local hot spots, by having the capability to add or remove heat almost instantaneously. Flow reactors also allow control over residence time, and control of the temperature and residence time can be utilized for minimizing the byproduct formation, and side reactions. This is immensely beneficial, particularly if a reaction creates more than one product. Achieving all these benefits require appropriate reactor design, mixing, heat sources/sinks, and monitoring and control systems. In addition to the right equipment, the CM can only be successful when supported by robust and scalable chemistry, systematic process design and efficient process analytical technology (PAT).

### System Integration and Equipment Sizing

The equipment sizing and telescopic process design should be performed in a synchronized fashion. In hybrid processes the design flexibility is higher. The steady state simulations can be used for evaluating the process performance at different scale and set-up, reduce inefficiencies, and improve the process flow. For such telescopic systems, the individual equipment sizing, then entire process train will be modelled for design space characterization and defining CPPs. Further evaluation of the process performance by models, and validating by some experiments, can be used for process optimization and scaling up, number up, our scaling out (4).

### Feeding Systems

The input materials and precursors can be solid, gas and liquid. Conventional pumps and gas cylinders and manifolds could provide the reliable supply of feed for long time. However, solids would need to dissolve in a solvent prior to feeding. In most cases, two dissolution tanks will be used, one is charging with solvent and solids and stirring for a required time to reach homogeneity, and one at service. Inline filters will be used to ensure capturing any undissolved particle entering the system (6).

### Heating or Cooling

The material can be heated or quenched in an individual step or in the reactor. The intensified process provides robust control on temperature. Heat sources can be by radiation (microwave, laser, light) or heat exchanger by a medium

### Reactors

The reactors come in different designs, shapes, geometry, and materials, but conventionally are PFR or CSTR.

The "larger" sizes PFRs and CSTRs require a mixing tool. The microreactors with 2-5 mm ID normally do not required internal static mixers. Although the flowrates are normally very low (low Reynolds number), the small tube diameter creates a fast radial diffusion and low radial dispersion. Smaller dimensions of the reactor result in a well-defined laminar flow regime. Typical for that is the parabolic flow profile with a broad residence time distribution. The dispersion is mostly axial, however, in most of the coiled tubes the Dean's flow effect enhance the radial mixing (7). For larger tubes (more than 7mm ID), and especially with multiphase systems, internal segmented mixers, or other mixing tools will be used. CSTRs are less common in flow-chemistry, but some processes use cascade CSTRs and also for combined steps, such as reactive crystallization. Single CSTRs have broad residence time distributions and low conversion rates per unit volume. For detail discussion on choosing between CSTRs, PFRs, and microreactors and characteristics refer to (4).

### Separation and Work-up

Continuous filtration (membrane or LLE), distillation, chromatography columns (simulated moving bed), and continuous crystallization are well-developed for different applications and available at various scales. The continuous crystallization is one of the most critical steps of the process, since most of the CQAs can be altered here. Impurity entrapping in the crystals, or change of particle size distribution, polymorph change, solvate channel formation, encrustation and process stability issues are all made this step challenging and critical. Two main types of the continuous crystallizers are Mixed Suspension Mixed Product Removal (MSMPR) and Oscillatory Baffled Crystallizers (OBC). Interested readers can refer to the Handbook of Continuous Crystallization for further details (8).

### Dynamic Process Modelling and Control

Mechanistic process modelling and simulation tools are

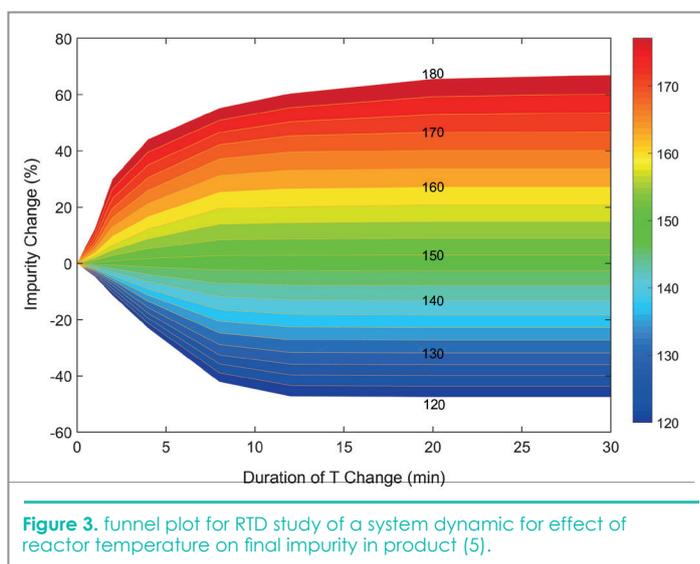


Figure 3. funnel plot for RTD study of a system dynamic for effect of reactor temperature on final impurity in product (5).

being used for dynamic simulation of the process. A low-level dynamic process model also can be empirically evaluated by extensive experimental study and generation of disturbances. The benefit of dynamic simulations is for defining system dynamic and evaluating how the entire process would respond to process disturbances, such as change in temperature or flow rates of entering materials, and finally defining process control strategies. The sensitivity analysis for CQAs of final product, for example impurity level, in response to CPPs is a crucial practice to ensure process stability and robustness (Figure 3).

### Correlating CMA to CPP to CQA

Lot to lot variation in starting materials, known as CMA variation, can impact the overall process. Analysing the correlation of CMAs to CPPs to CQAs is a backward practice, starting from CQAs of the final product to the start of the process. For instance, setting threshold of impurity level in final crystallize material defines the crystallization step performance, how to operate the crystallizer and how to control CCPs of the crystallizer (i.e. growth rate control by antisolvent addition rate) to reject as much impurity as possible. Then the incoming impurity concentration to the crystallizer (CMA for the crystallizer) will be defined by previous steps such as the distillation performance. Consecutively, the impurity generation variation is defined in the reaction step, which depend on temperature, residence time and concentration (flow-rate) of starting materials. The beforementioned sensitivity analysis defines the importance of each CPP and guide system designers or operator for proper control decisions and actions.

### Monitoring and Control Systems, PAT tools

There is also continuous monitoring of the quality by online or offline sensors, so parameters can still be fine-tuned during the operation in order to obtain the best product quality. The PAT tools and monitoring and control systems need their own substantial subject coverage which is beyond the scope of this work.

### FURTHER READING AND EXTENSION OF THE DISCUSSION

This short article cannot cover all the aspects of the CM of APIs. There are several remaining important features that can be discussed in future works. Some of them are: the PAT tools, End-to-End CM vs hybrid system, surge vessels and buffer tanks sizing, RTD study, types of disturbances and control strategies, GMP considerations and regulatory approaches, batch/lot definition, data management, control system

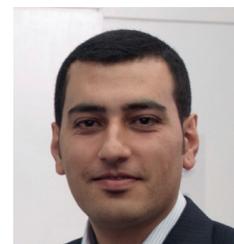
design, process validation, flexible manufacturing, and start-up and shutdown, and techno-economical analysis.

### REFERENCES

1. Akwi, F.M. and P. Watts, *Continuous flow chemistry: where are we now? Recent applications, challenges and limitations*. Chemical Communications, 2018. **54**(99): p. 13894-13928.
2. Berton, M., et al., *Scaling continuous API synthesis from milligram to kilogram: extending the enabling benefits of micro to the plant*. Journal of Flow Chemistry, 2020. **10**(1): p. 73-92.
3. Chanda, A., et al., *Industry Perspectives on Process Analytical Technology: Tools and Applications in API Development*. Organic Process Research & Development, 2015. **19**(1): p. 63-83.
4. Laporte, T.L., C. Wang, and S. Jones, *Process Development and Case Studies of Continuous Reactor Systems for Production of API and Pharmaceutical Intermediates*, in *Chemical Engineering in the Pharmaceutical Industry*, D.J.a. Ende, Editor. 2011, John Wiley & Sons, Inc. p. 319-339.
5. Yazdanpanah, N., T. O'Connor, and C. Cruz, *Dynamic Modeling of a Continuous Reactive Crystallization Process*, in *AICHE Annual Meeting 2018*. 2018, AIChE: Pittsburgh, PA, USA.
6. Hu, C., et al., *Development of an automated multi-stage continuous reactive crystallization system with in-line PATs for high viscosity process*. Reaction Chemistry & Engineering, 2018. **3**(5): p. 658-667.
7. Minnich, C.B., et al., *Determination of the Dispersion Characteristics of Miniaturized Coiled Reactors with Fiber-Optic Fourier Transform Mid-infrared Spectroscopy*. Industrial & Engineering Chemistry Research, 2010. **49**(12): p. 5530-5535.
8. Yazdanpanah, N. and Z.K. Nagy, *The Handbook of Continuous Crystallization*. 2020: Royal Society of Chemistry.

## ABOUT THE AUTHOR

**Nima Yazdanpanah** is a consultant on advanced manufacturing and modeling and simulation in bio/ pharmaceutical and fine chemical industries. His area of expertise covers mathematical modeling, process simulation, particulate matters, process design, and advanced manufacturing. Previously Nima was a research scientist with FDA. He was appointed as a member of an expert team for advancement of emerging technologies to modernize pharmaceutical manufacturing. Nima was a postdoctoral research associate at MIT, Department of Chemical Engineering, and Novartis-MIT Center for Continuous Manufacturing. He has worked for six years in industry for R&D and process design sections. ■



Looking for capacity...

## Debottlenecking by Continuous Manufacturing

Mobile static mixing stations mounted on movable skids → space savings >90%

Short process times due to enhanced mass & heat transfer with stable quality

Increased safety due to reactor volume reduction

Reduced manpower due to easy automation

Low storage demand due to real-time release & online drumming



BOOK YOUR DEBOTTLENECKING WORKSHOP WITH US TODAY!

+43 3182 62626-0  
office@microinova.com  
www.microinova.com

Your innovative partner for  
efficient modular plant systems  
& continuous manufacturing!

chimica oggi

# CHEMISTRY TODAY

+ regular section: PHARMA HORIZON



ISSN 0392-839X CHOGDS

CORNING

Advanced-Flow™ Reactors

## Integrated Production System

Corning's Advanced-Flow™ Reactor (AFR)  
provide customers with complete turnkey  
solutions for industrial production



Corning S.A.S. Reactor Technologies  
7 Bis Avenue de Valvins | CS 70156 Samois sur Seine  
77215 Avon Cedex, France

Tel. + 33164697107 | Fax + 33164697059  
reactors@corning.com | [corning.com/reactors](http://corning.com/reactors)

© 2020 Corning Incorporated. All Rights Reserved.