Continuous Manufacturing to Improve Pharmaceutical Quality: Research Examples and Opportunities

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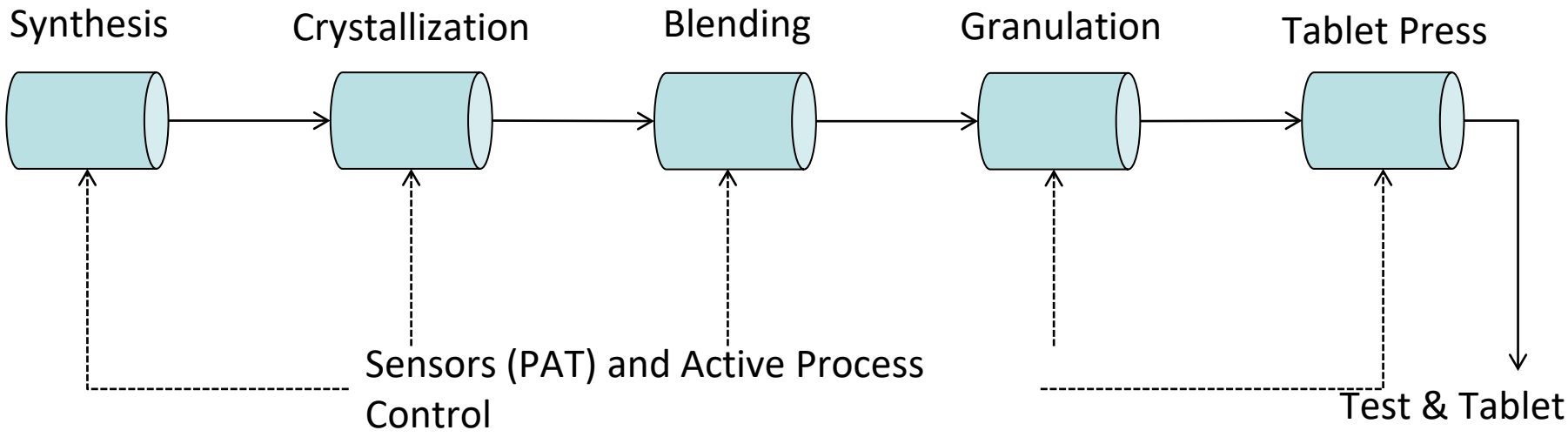
Pharmaceutical Quality Symposium 2023– November 1st, 2023

Outline

- Continuous manufacturing (CM) of drug substances and drug products
- Process modeling and simulation (M&S) for CM at FDA
- CM research highlights
- Opportunities of CM for generic drug products

CM of Drug Substance and Drug Product

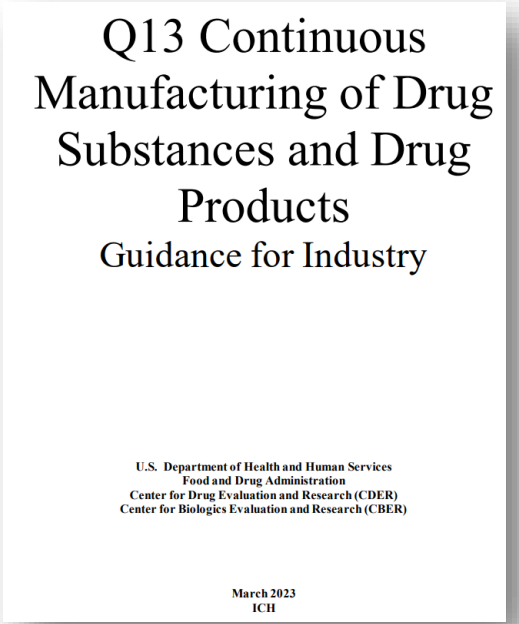


Benefits:

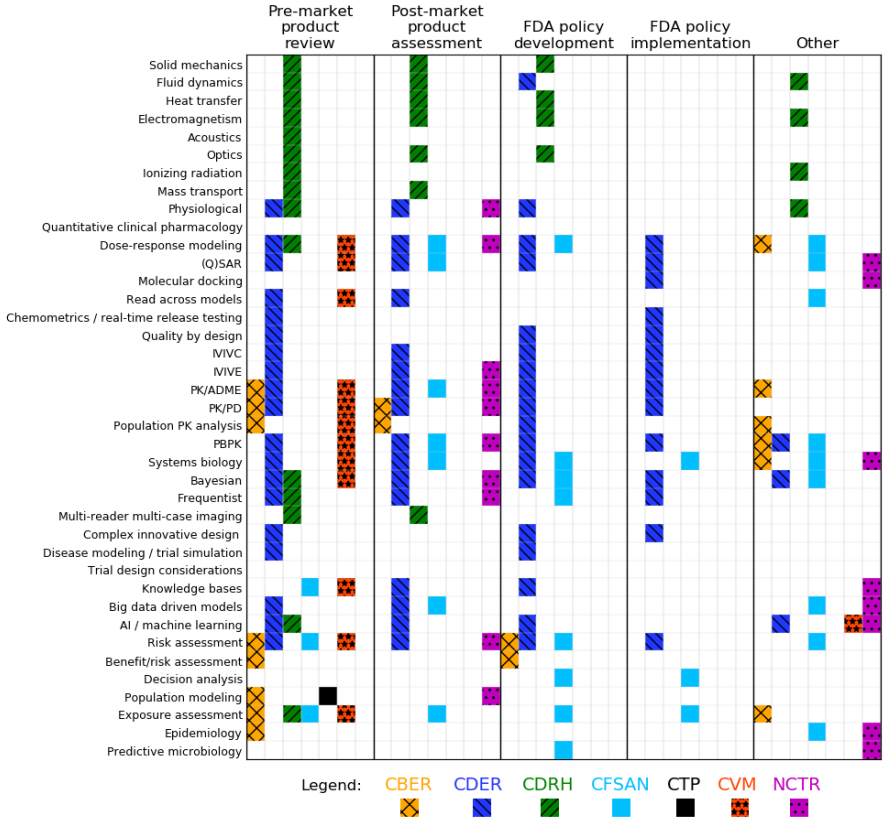
- Reduced environmental footprint
- Improved efficiency
- Enhanced product quality
- Faster time-to-market
- Cost savings

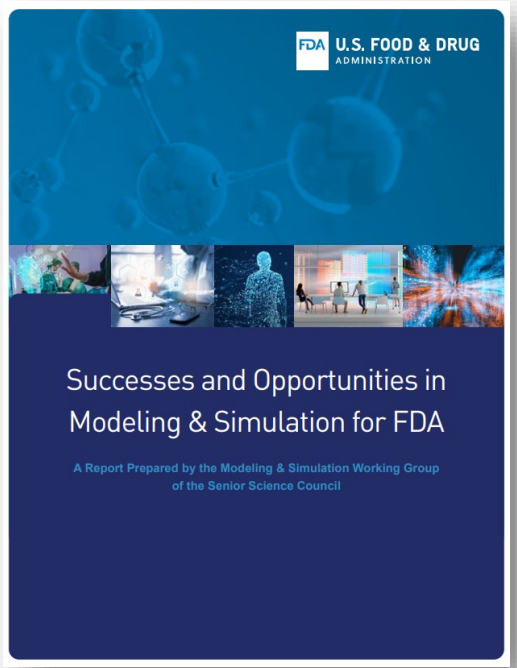
Regulatory Considerations on CM

- **Characterization of process dynamics for critical steps and integrated system**
  - Residence time distribution for a proposed mass flow rate
  - Understanding of the system response to transient disturbances
- **Evaluation of the proposed attributes and specifications of raw materials**
  - Impact of variations in material properties on the performance of CM and product quality
- **Process monitoring and control strategy**
  - Monitor and detect transient disturbances and process deviation
  - Frequency of PAT measurements
  - Active process controls
- **Material collection and diversion**
  - Start up and shutdown
  - Strategy to identify, isolate and divert non-conforming materials
- **Real-time release testing**
  - PAT tools for assay and content uniformity
  - Dissolution models



Modeling and Simulation (M&S) at FDA





November 2022

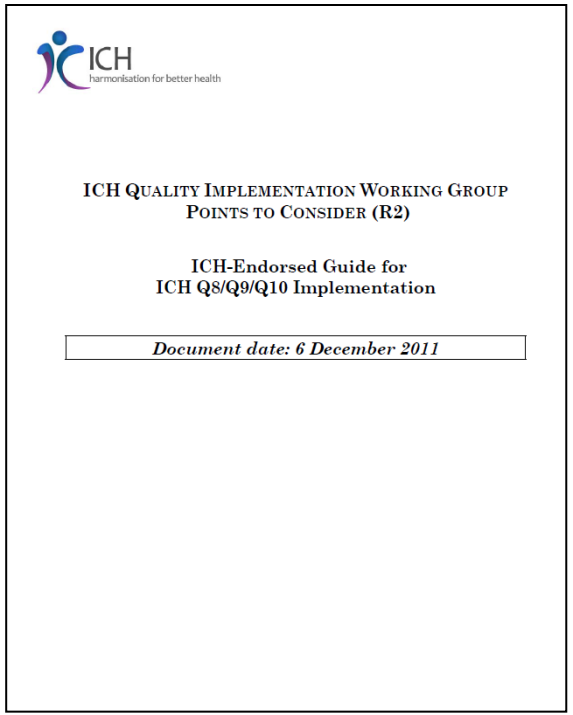
https://www.fda.gov/science-research/about-science-research-fda/modeling-simulation-fda

Process M&S for CM at FDA

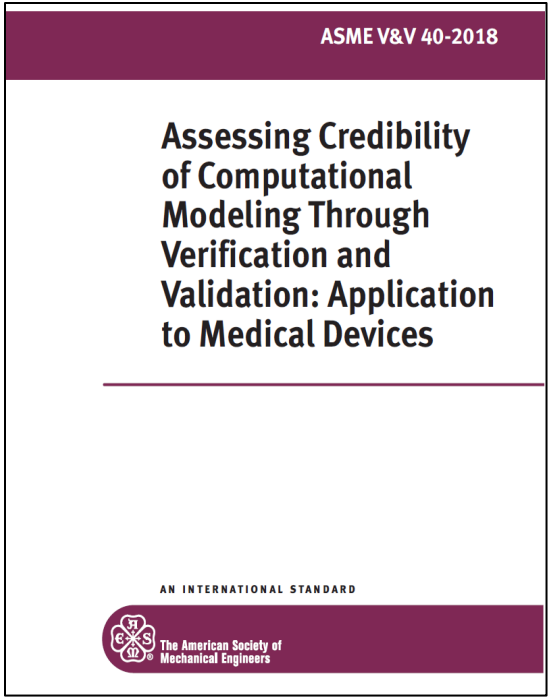
- Development and assessment of process models by OPQ is not unprecedented but the frequency, types of models, and applications are evolving
- Advanced manufacturing a potential driving force for utilization of process modeling
  - Inherently data rich processes
  - Availability of plant wide information systems
  - Implementation of advanced control strategy approaches (MPC, RtR, etc.)
- Office of Pharmaceutical Quality (OPQ) has developed internal process M&S capabilities:
  - Continuous API synthesis and crystallization
  - Continuous drug product manufacturing
- FDA has established multiple external collaboration in the area of process M&S (e.g., RCPE, Siemens, Rutgers, Purdue, MIT)

Regulatory Guidances for Establishing and Assessing Model Credibility

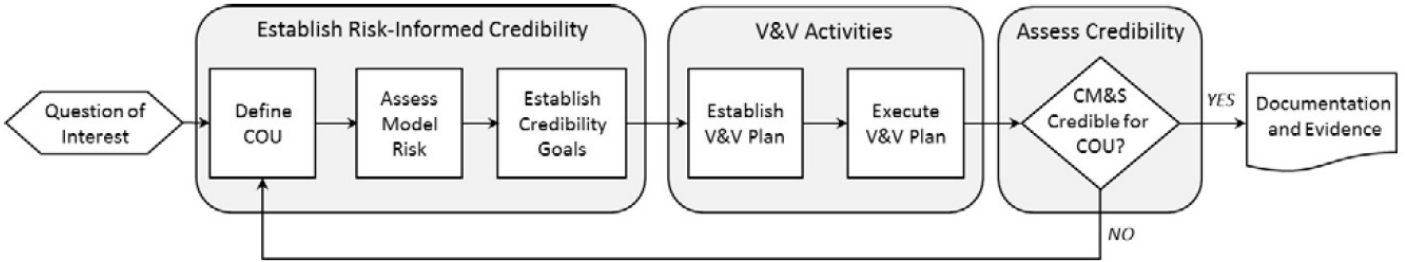
ICH Points to Consider Document



ASME V&V 40



ASME V&V 40 Risk-Informed Credibility Assessment Framework



- The **question of interest** describes the specific question, decision or concern that is being addressed
- **Context of use (COU)** defines the specific role and scope of the model used to inform that decision
- **Model risk** is the possibility that the model may lead to a false/incorrect conclusion, resulting in adverse outcomes
- **Model credibility** refers to the trust in the predictive capability of the model for the COU

Model Credibility Factors

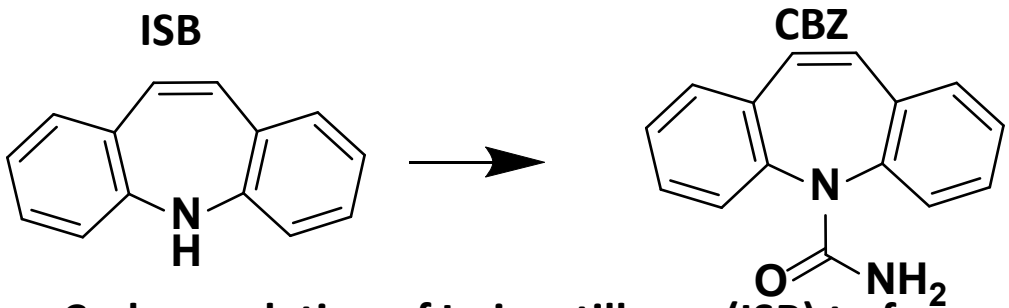
Model credibility can be established through the collection of V&V evidence and by demonstrating the applicability of the V&V activities to support the use of the model for the COU.

Credibility Factors																	
Verification					Validation									Applicability			
Code		Solution			Model				Comparator			Output Assessment					
Software Quality Assurance	Numerical Algorithm Verification	Discretization Error on	Use Error	Numerical Solver Error	System Configuration	System Properties	Boundary Conditions	Governing Equations	Sample Characterization	Control Over Test Conditions	Measurement Uncertainty	Equivalency of input Output types	Rigor of Output Comparison	Relevance of the Quantities of Interest	Applicability to the Context of Use		

Level	Description
1	Visual comparison concludes good agreement.
2	Comparison by measuring the difference between computational results and experimental data. Differences are less than 20%.
3	Comparison by measuring the difference between computational results and experimental data. Differences are less than 10%.
4	Comparison with uncertainty estimated and incorporated from the comparator or computational model. Differences between computational results and experimental data are less than 5%. Includes consideration of some uncertainty, but statistical distributions for uncertainty quantification are unknown.
5	Comparison with uncertainties estimated and incorporated from both the comparator and the computational model, including comparison error. Differences between computational results and experimental data are less than 5%. Statistical distributions for uncertainty quantifications are known.

Case Study I: CM of Carbamazepine (CBZ)

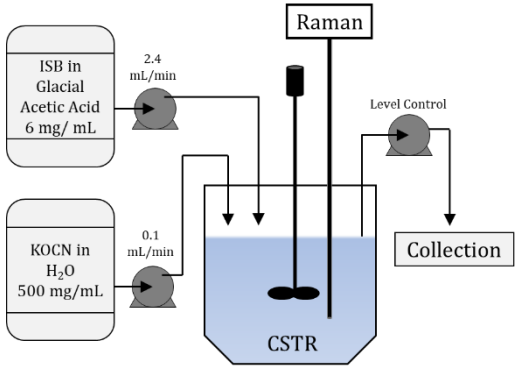
Developed an experimental platform and process models for continuous synthesis of CBZ with on-line PAT tools for advanced process monitoring and control

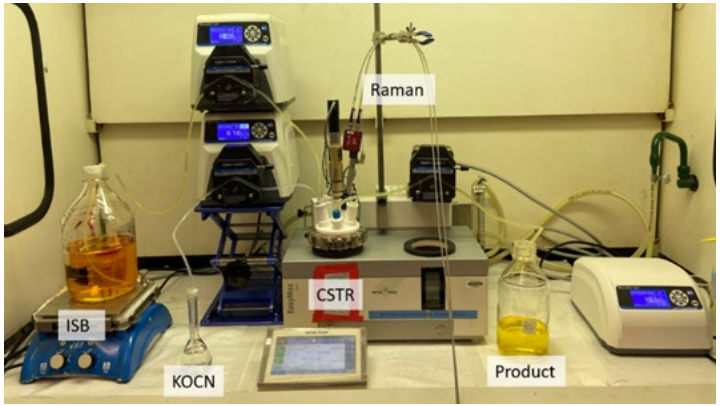


Carbamoylation of Iminostilbene (ISB) to form Carbamazepine (CBZ).

https://doi.org/10.1039/D2RE00476C

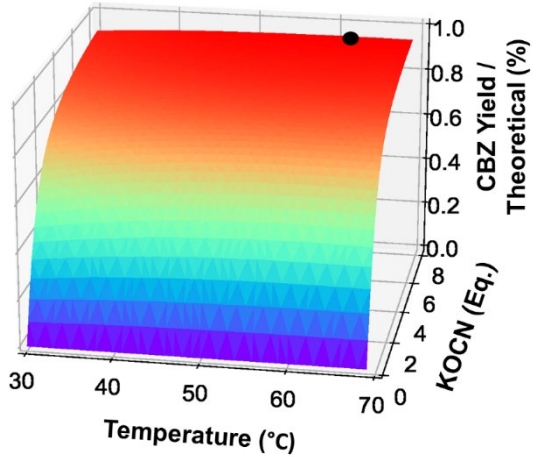
Modelling the Continuous Synthesis Process for CBZ

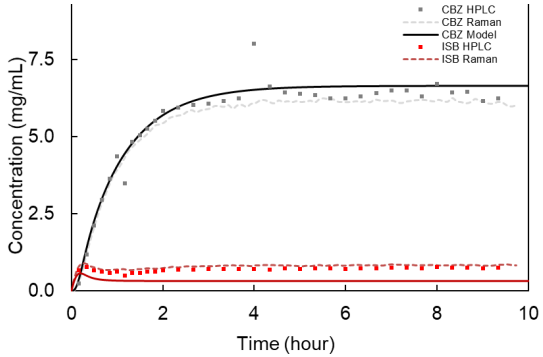




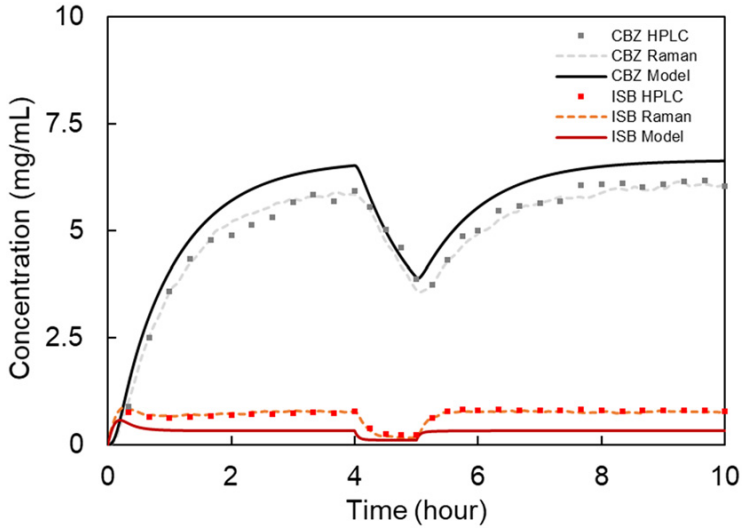
Global Kinetic Optimization for CSTR Process

Startup-Base Case Demonstration





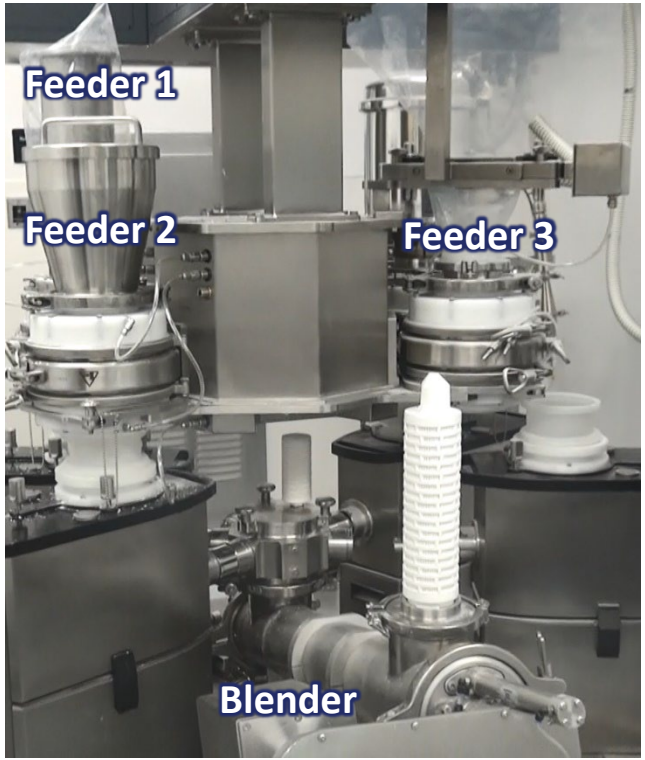
Modeling Process Disturbances

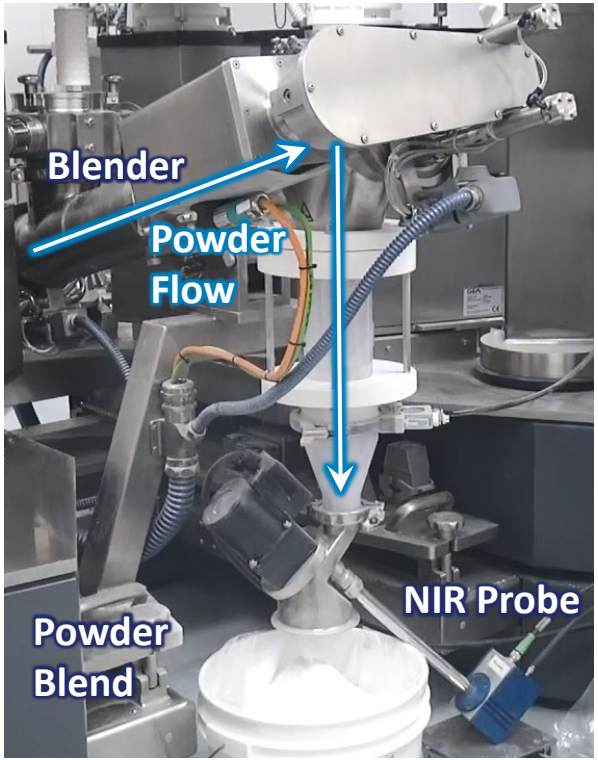


Stepwise disturbance in ISB stock:
6 mg/ml to 2 mg/mL from hour 4 to hour 5

Case Study II: Continuous Powder Blending

- Three loss-in-weight feeders feed API and excipients into a continuous blender
  - Blender contains configurable shaft with 28 elements
- Near infrared (NIR) spectrometer positioned below blender outlet
- The effects of material properties and process parameters on the residence time distribution (RTD) of API was investigated
- A discrete element method (DEM) blender model was developed and validated using experimental data

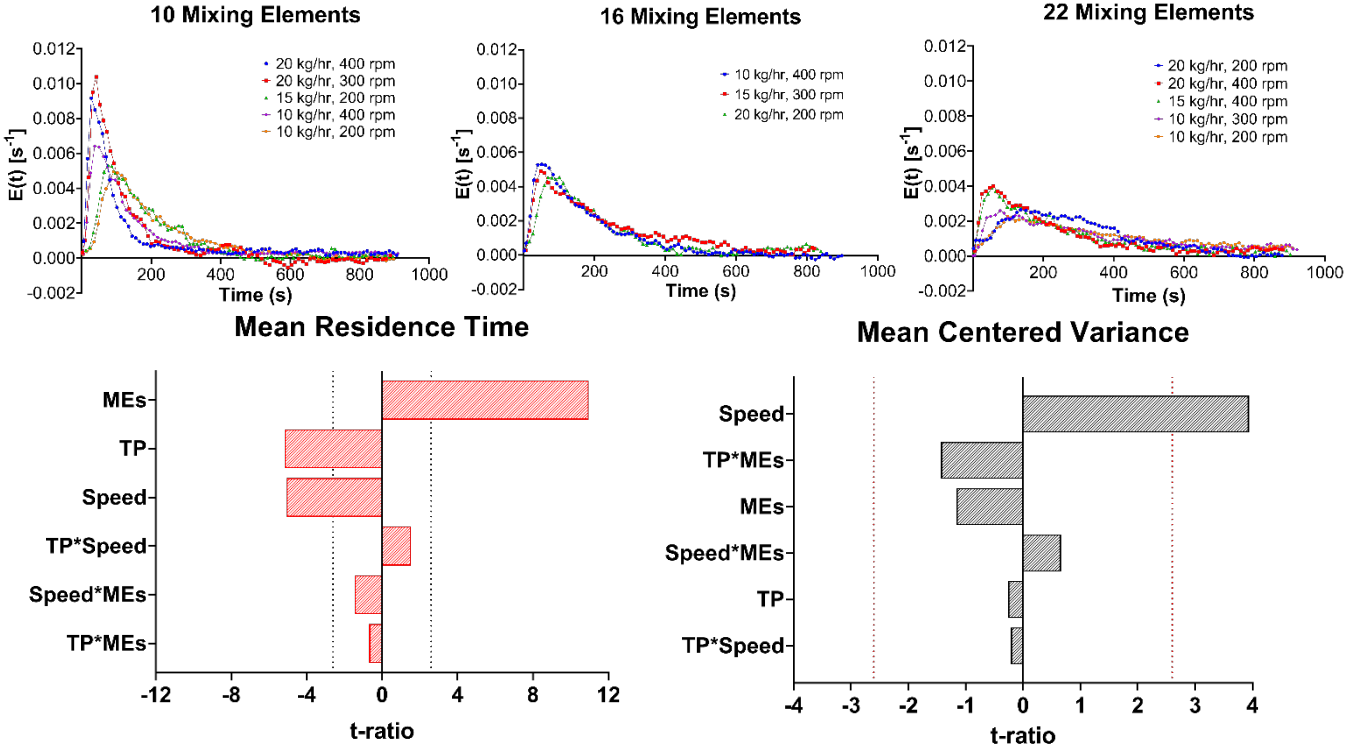




https://doi.org/10.1016/j.cherd.2022.12.005

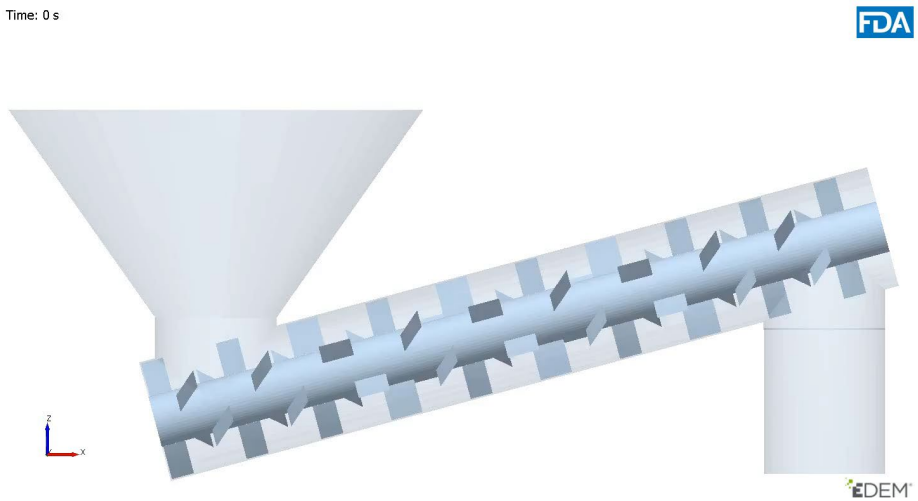
Effect of Process Parameters on RTDs

- Mean Residence Time:
  - Increased with additional mixing elements (MEs)
  - Decreased with increasing total throughput (TP) and blender speed (Speed)
- Mean Centered Variance:
  - Increased with increasing blender speed

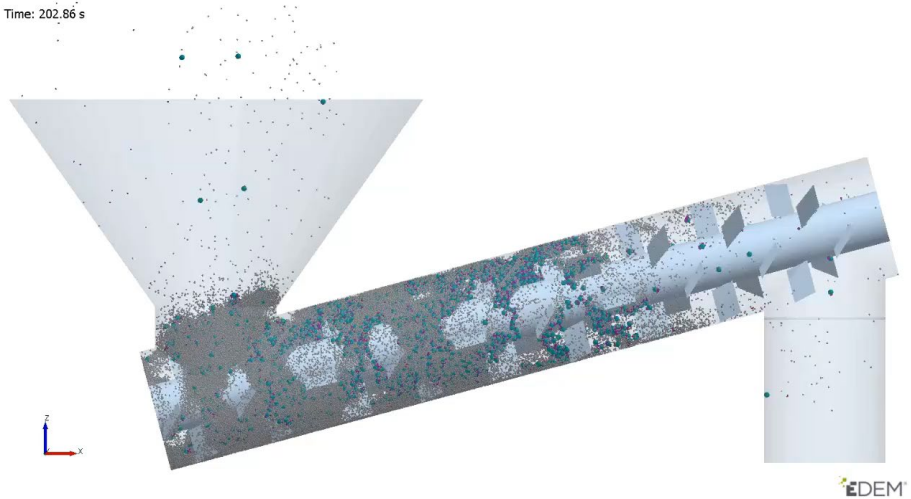


Assessing RTDs in Continuous Powder Blending using DEM

Initial state



Steady state

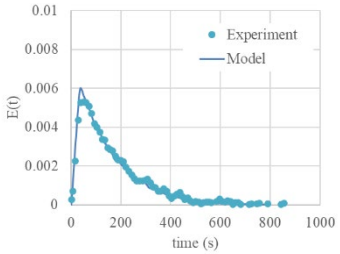


Videos are obtained from the simulation with 5%API, 15kg/hr, 300rpm, and 16M

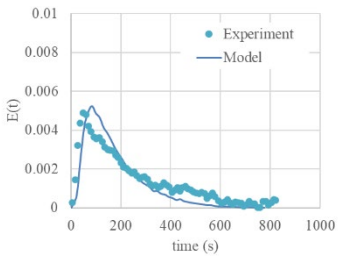
API – dark magenta, MCC – dark cyan, lactose – dark grey

DEM Model Validation

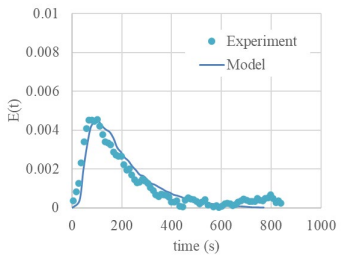
Case 5: 10kg/h, 400rpm, 16M



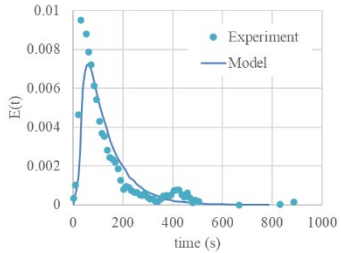
Case 6: 15kg/h, 300rpm, 16M



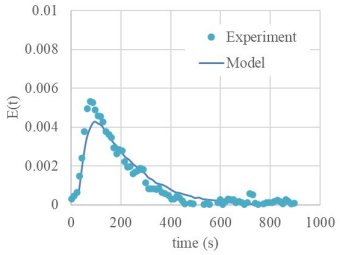
Case 7: 20kg/h, 200rpm, 16M



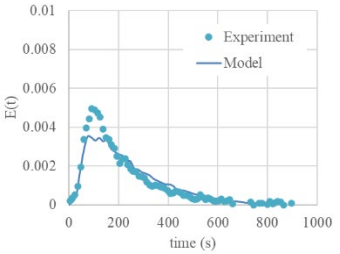
Case 9: 20kg/h, 300rpm, 10M



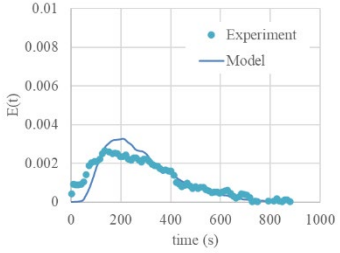
Case 10: 15kg/h, 200rpm, 10M



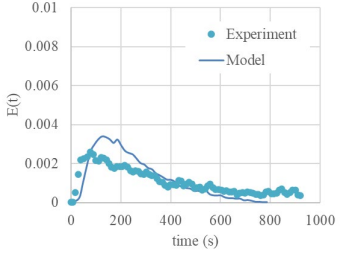
Case 12: 10kg/h, 200rpm, 10M



Case 13: 20kg/h, 200rpm, 22M



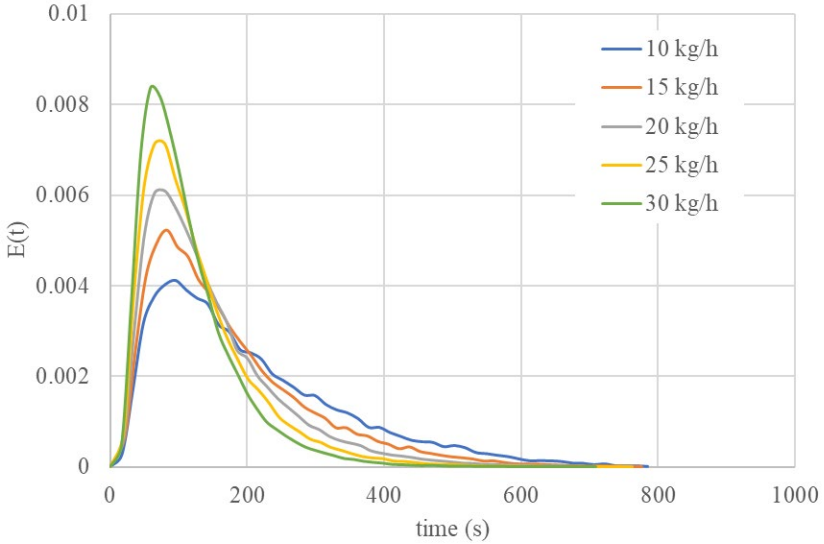
Case 16: 20kg/h, 400rpm, 22M

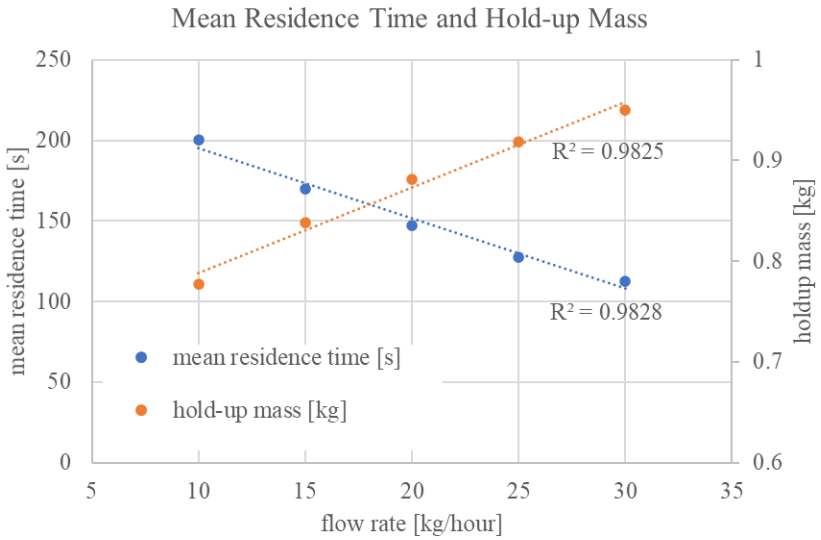


- Simulations agree well with experiments in most of cases

Effect of Throughput

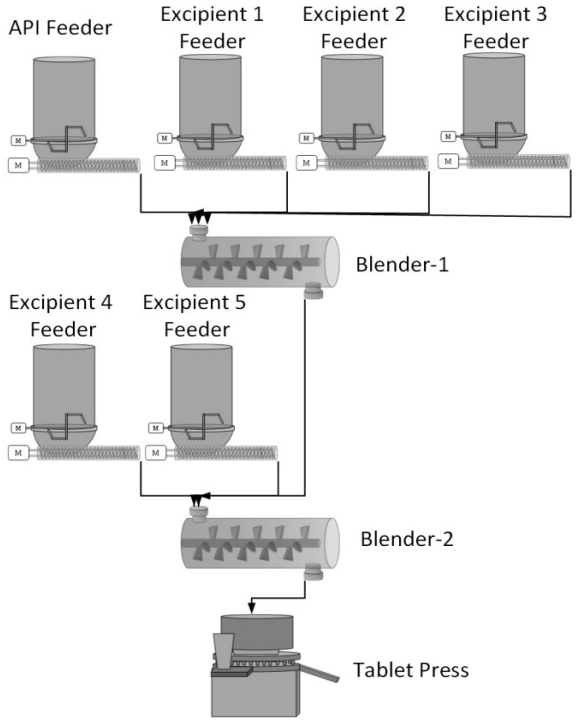
- Mean residence time decreases linearly with increasing throughput
- Hold-up mass increases linearly with increasing throughput





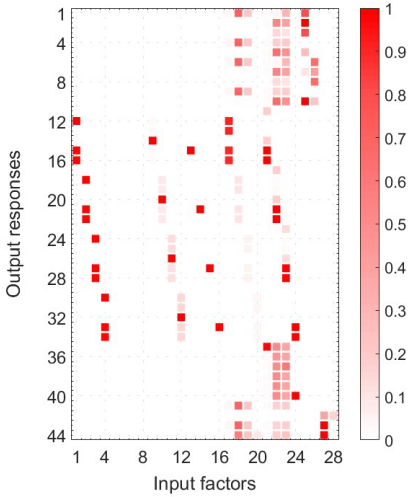
Case Study III: Quality Risk Assessment of Continuous DP Process

- Developed flowsheet process model for a continuous direct compression (CDC) line
  - Low dose formulation, excipient 1 and 2 compose over 90% of the formulation
- Performed sensitivity analysis in the risk assessment
- Identified potential process parameters and material attributes that affect critical quality attributes of the drug product

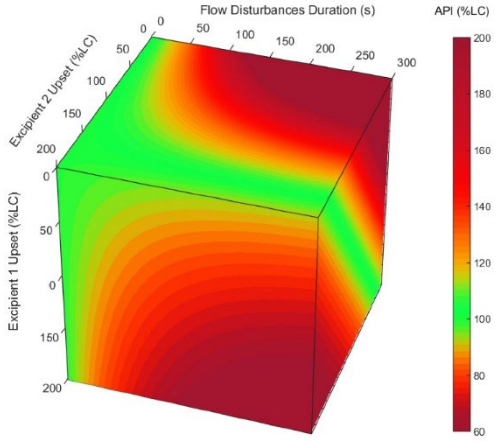


https://doi.org/10.1016/j.compchemeng.2019.06.033

Sensitivity Analysis of CDC Process



Intensity plots representing steady-state sensitivity analyses that capture the effects of input factors on the output responses



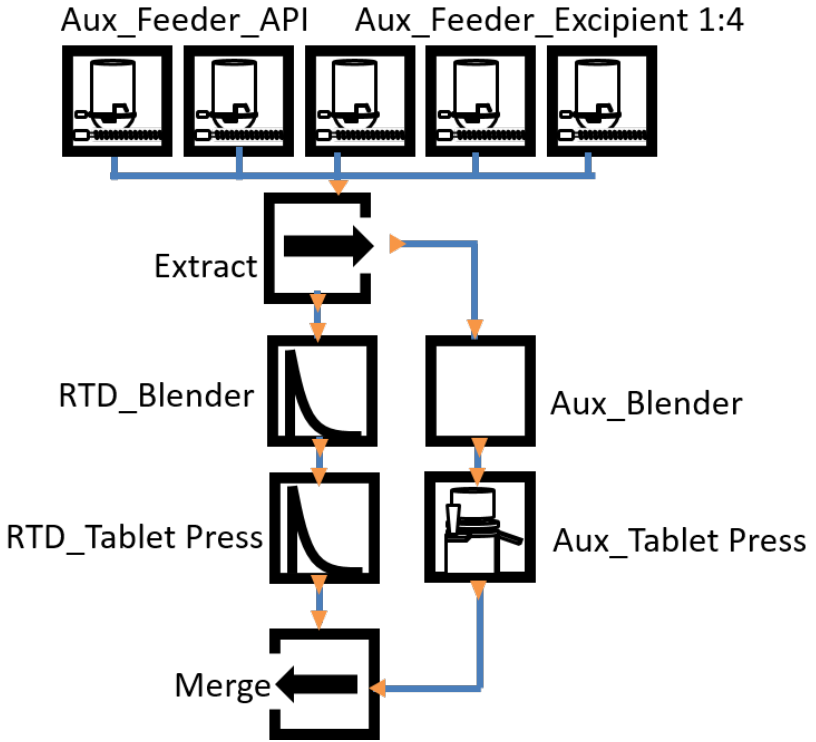
Impact of simultaneous disturbance in the flowrates of excipients 1 & 2 on final product concentration

API and excipients 1&2 density, and their flowrates are significant factors impacting drug product quality

Case Study IV: Quality Risk Control of a Continuous DP Process

- Developed a RTD-based process modeling framework for a CDC line
  – Excipients 1 -4 compose over 65% of the formulation

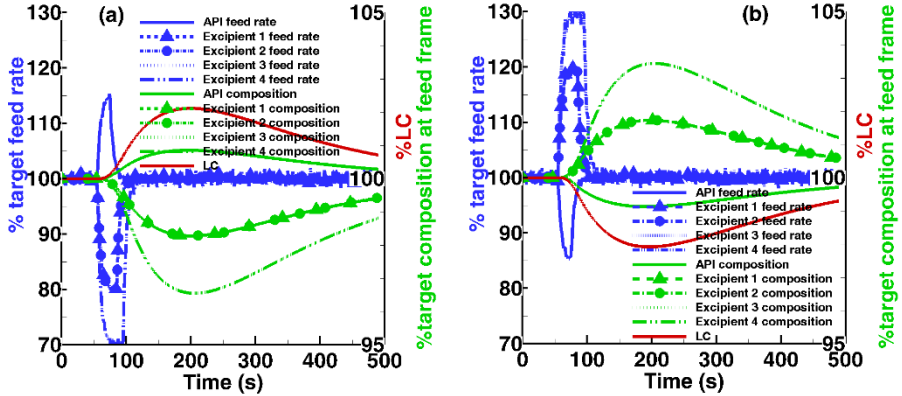
- The effectiveness of in-process control (IPC) strategies were evaluated



https://doi.org/10.1208/s12249-020-01913-8

Establishing IPC Limits for API Loading

- Two worst-case scenarios are considered to evaluate proposed IPC limits
  - API feeder operates at its upper (Fig. a)/lower limit (Fig. b) and excipients feeders operate at their lower (Fig. a)/upper limits (Fig. b)



- The feeder IPC limits are set conservatively as the corresponding peak concentrations at the feed frame are within the feed frame IPC limits

Component	Feeder IPC Limits	Feed Frame IPC Limits
API	±15% for 20 seconds	±5%
Excipient 1, 2	±20% for 30 seconds	±5%
Excipient 3, 4	±30% for 40 seconds	±10%

Opportunities of CM for Generic Drug Products

- 90% of medicines used by U.S. patients are generic, but no generic medicines have been approved to use CM

- One of the potential drivers motivating generic companies to be involved in implementing CM includes complex drug products such implants, long-acting microspheres, and liposomes

- CM applicants had shorter times to approval and marketing compared to batch applicants
  - 3 months faster to approval (median)
  - 4 months faster to marketing
  - ~$171-537M in early revenue benefit

- No substantial regulatory barriers for CM related to:
  - Manufacturing process changes
  - Pre-approval inspections

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An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US

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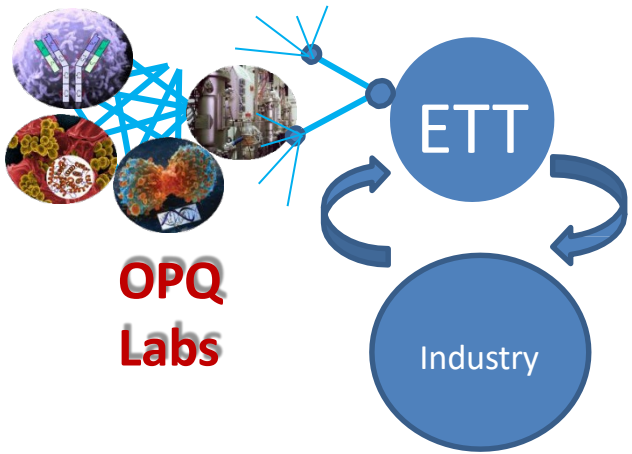
ABSTRACT

Continuous manufacturing (CM) sends materials directly and continuously to the next step of a process, eliminating hold times and reducing processing times. The potential benefits of CM include improved product quality, reduced waste, lower costs, and increased manufacturing flexibility and agility. Some pharmaceutical manufacturers have been hesitant to adopt CM owing to perceived regulatory risks such as increased time to regulatory approval and market entry, more difficulty submitting postapproval changes, and higher inspectional scrutiny. An FDA self-audit of regulatory submissions in the U.S. examined the outcomes, at approval and during the product lifecycle, of continuous manufacturing applications as compared to traditional batch applications. There were no substantial regulatory barriers identified for CM applications related to manufacturing process changes or pre-approval inspections. CM applicants had relatively shorter times to approval and market as compared to similar batch applications, based on the mean or median times to approval (5 or 3 months faster) and marketing (12 or 4 months faster) from submission, translating to an estimated $171-537 M in early revenue benefit.

https://doi.org/10.1016/j.ijpharm.2022.121778

Concluding Thoughts

- Regulatory experience for advanced manufacturing is evolving
- Research Case Studies Support Regulatory Decision Making
    - OPQ Science and Research
        - Knowledge gained from the internal and sponsored research inform policy, review, and inspection activities, ensuring that FDA regulatory policies reflect state-of-the-art manufacturing science.
- Shared learning and open communication to accelerate adoption of emerging technologies to advance product quality



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