PQRI Workshop:
Managing Excipient and API Impact on Continuous Manufacturing
May 17 – 18, 2022

FDA U.S. FOOD & DRUG ADMINISTRATION

Leveraging Residence Time Distribution (RTD) Models to Understand Ingredient and Process Impacts in Continuous Manufacturing

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Disclaimer

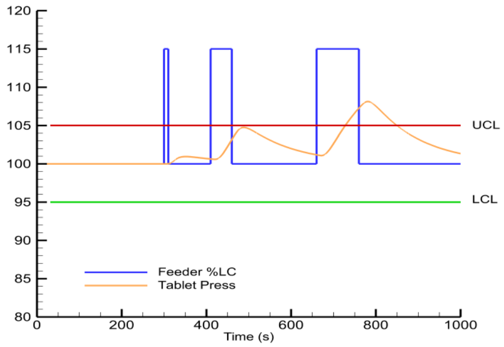
- This presentation reflects the views of the authors and should not be construed to represent FDA’s views or policies.

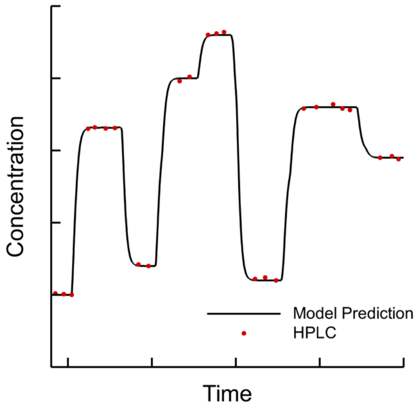
Process Dynamics

- The dynamics of how materials or disturbances flow through the process is a critical aspect of **process understanding**
  - Identify typical failure modes or deviations (long term vs. short term; e.g., feeder variability)
  - Evaluate response to set point changes (e.g., change in line rates)
  - Assess the impact of startup and shutdown on material quality
- Material feeding variation of formulation components can translate into drug content uniformity variation
  - The amplitude and frequency of variations in the component feed rates and the capability of the process to dampen these variations must be fully understood
- Obtain an **understanding of process dynamics** by characterizing the Residence Time Distribution (RTD)
  - RTD is a probability distribution that describes the amount of time a mass or fluid element remains in a process

Utilization of RTD in Control Strategy for CM

- **Supporting Sampling Strategy**
  - Detectability of transient disturbances impacted by the relationship between process dynamics and sampling frequency
- **Material Traceability**
  - Understanding of propagation of a disturbance between extraction points in the system is important to justify the amount of material at risk due to a disturbance
- **Process Monitoring**
  - Predicting blend concentrations based on measured input feeding variability

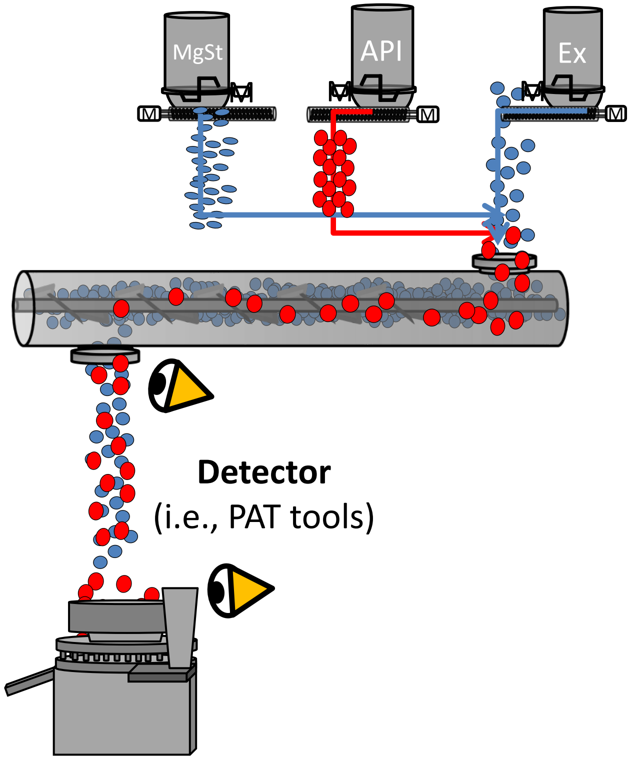




Assessment of data submitted on RTD will depend on how it is used in the control strategy

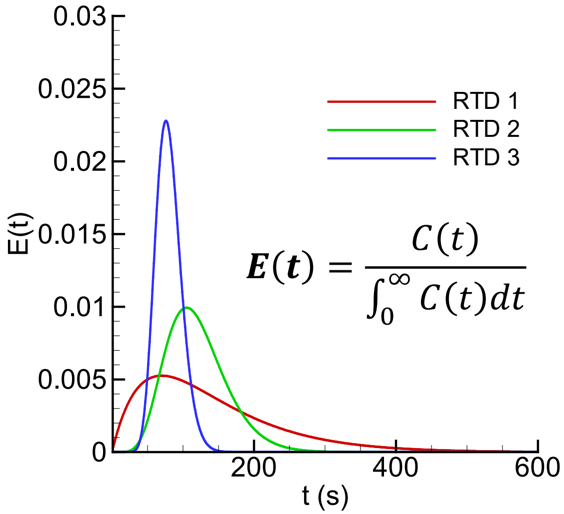
Characterizing Continuous Processes

- Continuous feeders dispense material (API, excipients) into unit operations
- System is allowed to reach steady state
- Tracer material is introduced into system
    - Pulse or step change
    - API typically used as tracer
- PAT tools located downstream measure concentration of tracer exiting process as a function of time



RTDs and Their Characterization

- A **Residence Time Distribution** (RTD) is a probability distribution that describes how long material spends in a process
  - Well-established engineering approach for non-ideal flow
- RTDs have been shown to depend on material properties, process parameters, and equipment configuration
- RTDs [*E(t)*] can be characterized by moments describing their shape
  - **Mean Residence Time** (MRT, τ) is the average amount of time material spends in the system
  - **Mean Centered Variance** (MCV, σ_τ^2) describes the width of the distribution (i.e., the amount of back-mixing)



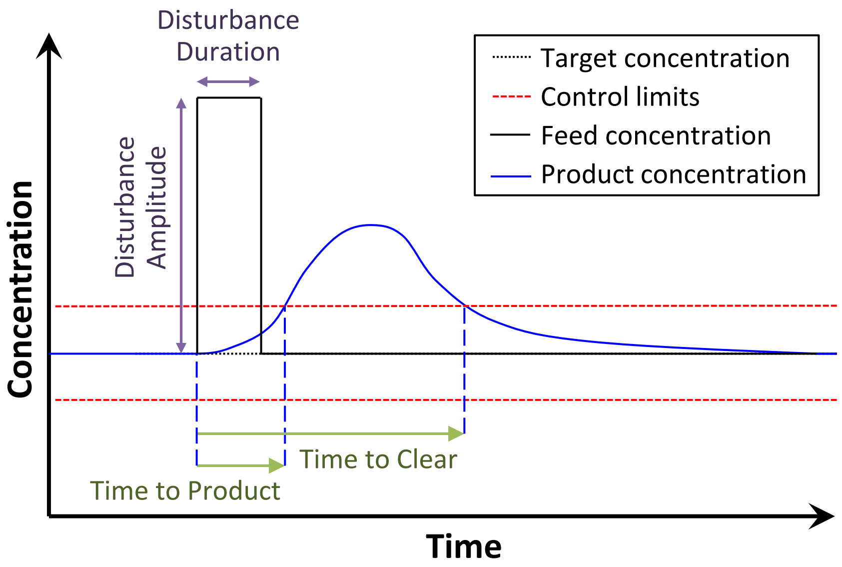
$$\boldsymbol{E(t)} = \frac{C(t)}{\int_0^\infty C(t)dt}$$

$$\boldsymbol{MRT} = \tau = \int_0^\infty t \cdot E(t)dt$$

$$\boldsymbol{MCV} = \sigma_\tau{}^2 = \int_0^\infty \frac{(t-\tau)^2}{\tau^2} E(t)dt$$

CM Process Control Using RTDs

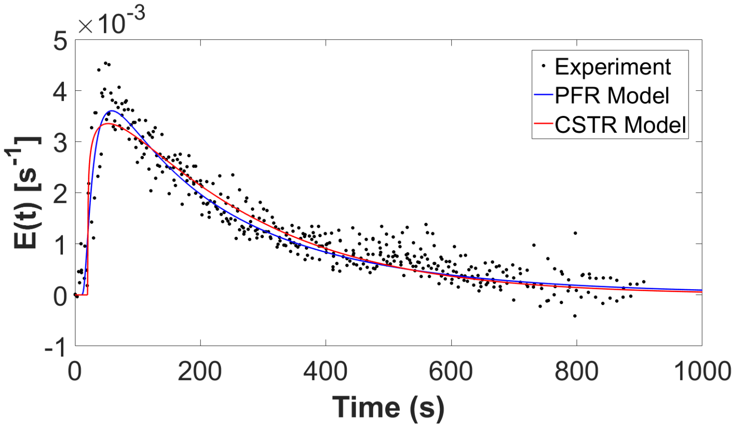
- Isolation and rejection of non-conforming material is a critical aspect of CM process control strategy
  - Planned process start-ups and shut-downs
  - Temporary process disturbances or upsets
- Material diversion points can be placed downstream of detectors, subjected to feed-forward control
- RTDs provide an understanding of how fast disturbances propagate and spread through a system
  - Enables real-time prediction of feeding material disturbances on blend and content uniformity



- **Time to Product:** Time it takes for first material impacted by disturbance to reach diversion point
- **Time to Clear:** Time it takes for all material impacted by disturbance to reach diversion point, at which time the process should be back within a state of control

Residence Time Distribution Models

- RTDs commonly fitted to two models
  - **Axial Dispersion Model**
    - Plug flow reactor (PFR) with back-mixing
    - Peclet number (*Pe*) describes degree of dispersion
    - Best suited for cases of low dispersion
  - **Tanks-in-Series Model**
    - Chain of continuous stirred-tank reactors (CSTRs)
    - Theoretical number of tanks (*N*) describes degree of dispersion
  - Both models also estimate MRT (τ) as a fitting parameter of dimensionless time:
    - $\theta = \left(t - t_{lag}\right)/\tau$
- A good model fit does not necessarily imply fitting parameters are accurate

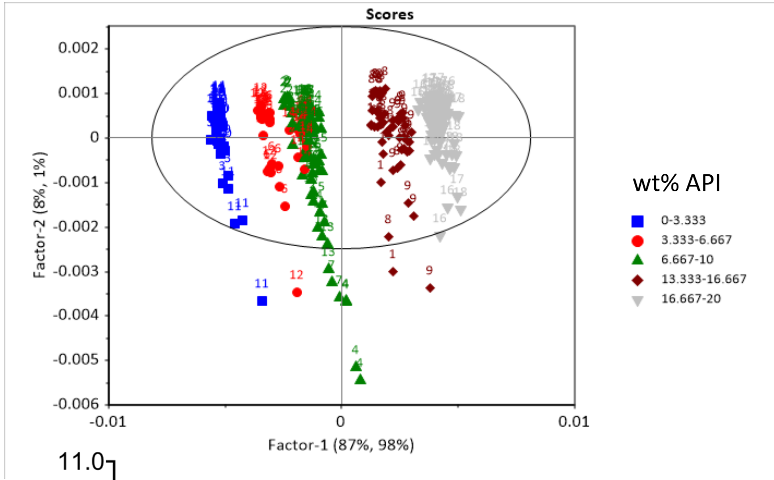


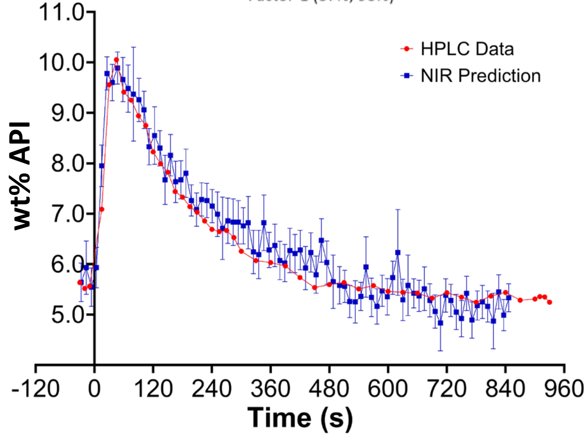
$$\tau E_{PFR}(t) = \begin{cases} 0, & t \le t_{lag} \\ \sqrt{\dfrac{Pe}{4\pi\theta}} * exp\left(-\dfrac{Pe[1-\theta]^2}{4\theta}\right), & t > t_{lag} \end{cases}$$

$$\tau E_{CSTR}(t) = \begin{cases} 0, & t \le t_{lag} \\ \theta^{N-1}\dfrac{N^N}{\Gamma(N)} * exp[-N\theta], & t > t_{lag} \end{cases}$$

PAT Data Collection and Model Development

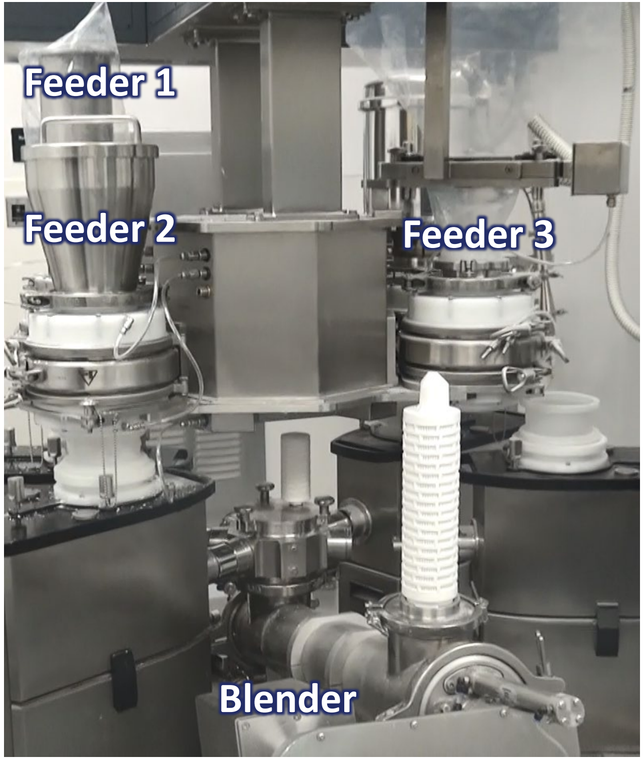
- PAT calibration model(s) established under controlled conditions mimicking the in-line process measurements as closely as possible
  - Capture appropriate component concentration ranges and possible sources of variability (e.g., process, analyzer, material characteristics)
  - Equivalent sample presentation conditions
- Multivariate models may be employed to estimate sample characteristics from spectral variation
  - Model parameter selection (e.g., pretreatments, wavelength range, number of factors) should consider both predictive performance and model robustness
  - External validation with independent samples representative of the commercial process

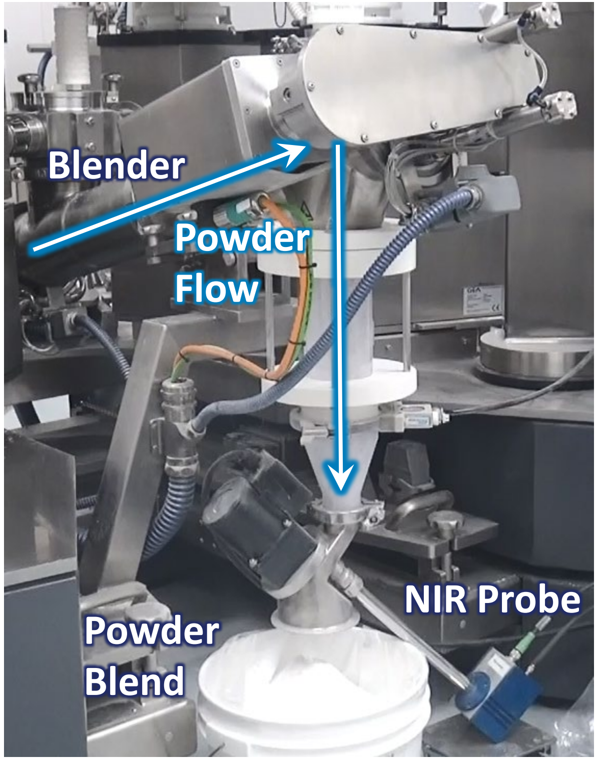




Continuous Feeding and Blending Unit

- Three loss-in-weight feeders feed API and excipients into a continuous tubular blender
- Blender contains configurable shaft with 28 elements
  - Either transport or mixing
  - 2 blades per element
- Near infrared (NIR) spectrometer positioned below blender outlet

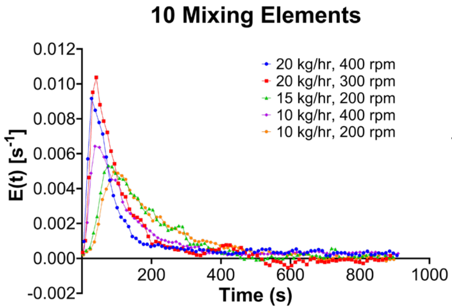


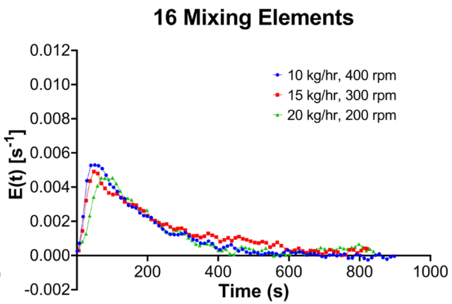


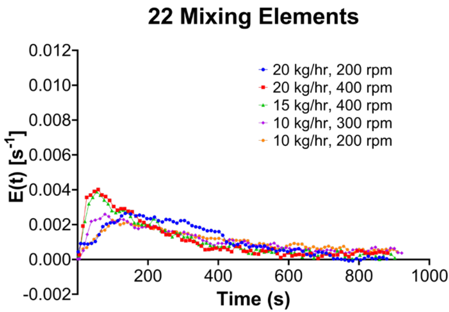
Continuous feeding and blending unit used to perform experiments

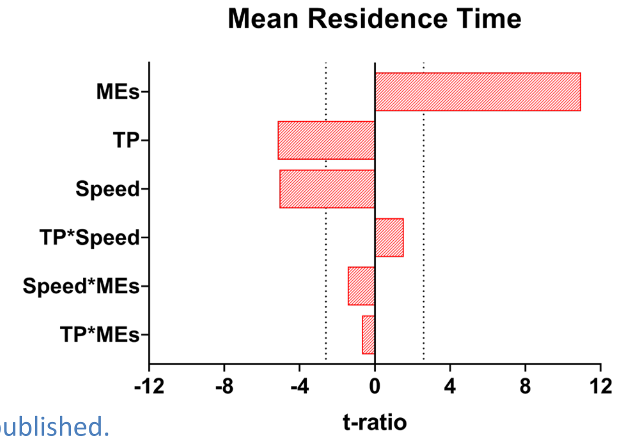
Effect of Process Parameters on RTDs

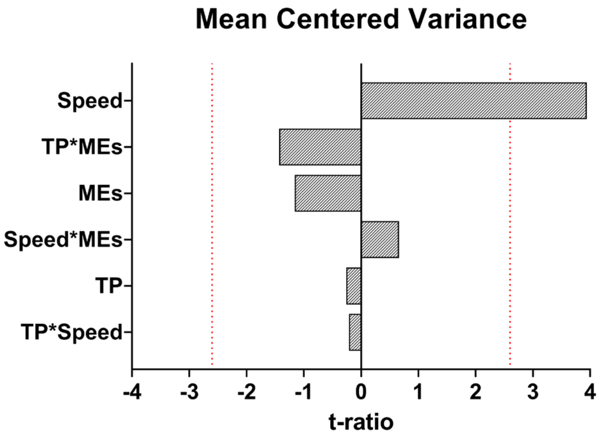
- Mean Residence Time:
  - Increased with additional mixing elements (MEs)
  - Decreased with increasing total throughput (TP) and blender speed (Speed)
- Mean Centered Variance (i.e., pulse dispersion):
  - Increased with increasing blender speed











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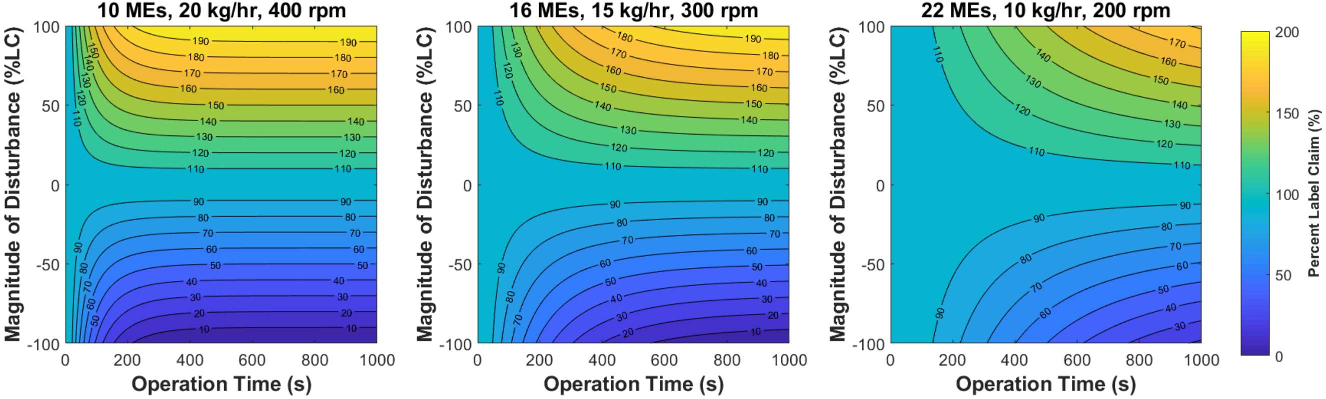
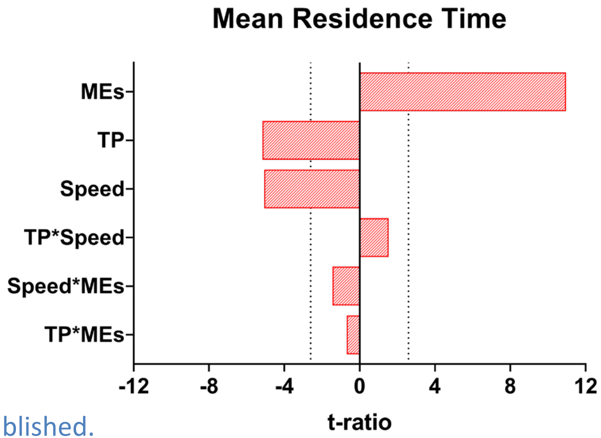
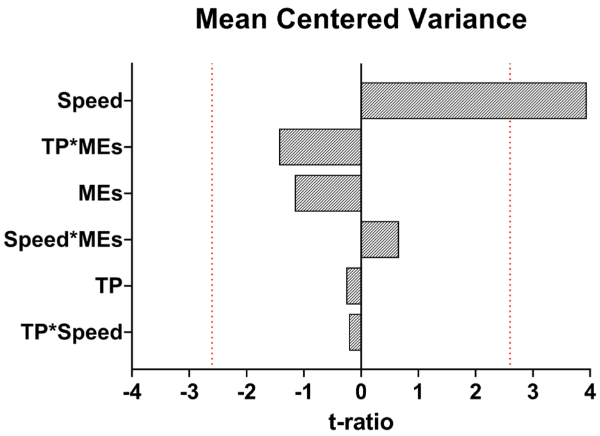
Effect of Process Parameters on RTDs

- Mean Residence Time:
  - Increased with additional mixing elements (MEs)
  - Decreased with increasing total throughput (TP) and blender speed (Speed)
- Mean Centered Variance (i.e., pulse dispersion):
  - Increased with increasing blender speed
- Most operating flexibility using settings with high mean residence time







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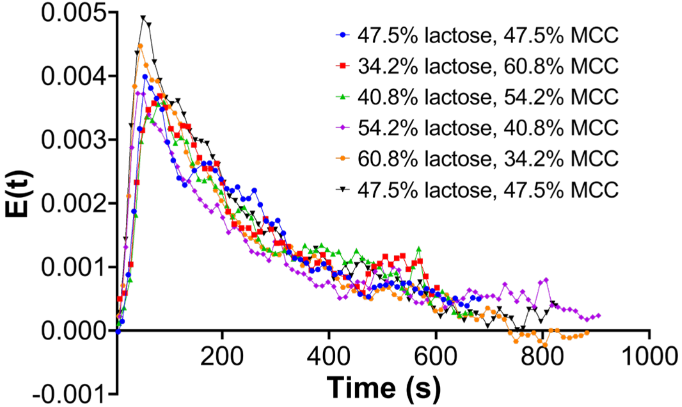
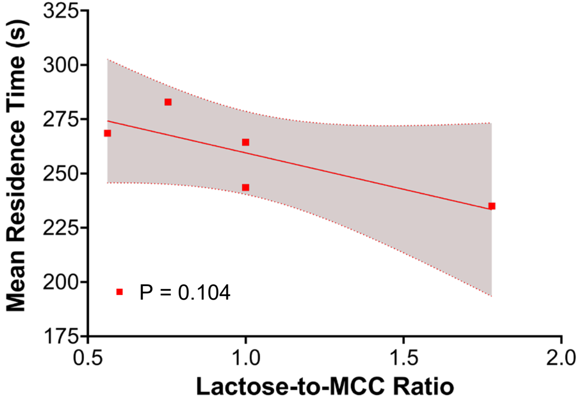
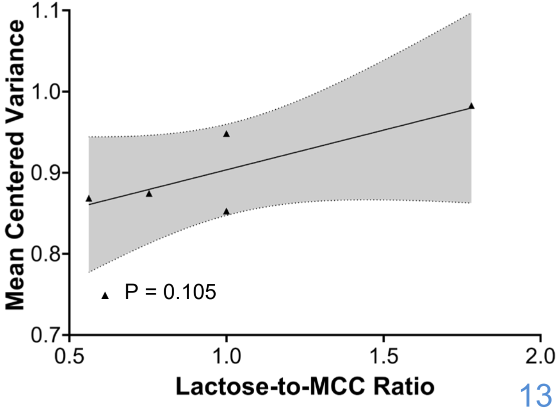
Effect of Bulk Material Properties on RTDs

- Varied excipient ratio at fixed process conditions and API flow rate
  - Lactose more cohesive with higher bulk density, MCC free flowing with lower bulk density





- Bulk properties should be considered when evaluating RTDs
  - Increasing lactose-to-MCC ratio (higher bulk density, cohesion) slightly decreased MRT and increased MCV (both $P \approx 0.10$)
  - Understanding the impact of the shift in MRT and MCV can be demonstrated by evaluating the impact of bulk material properties on dampening disturbances



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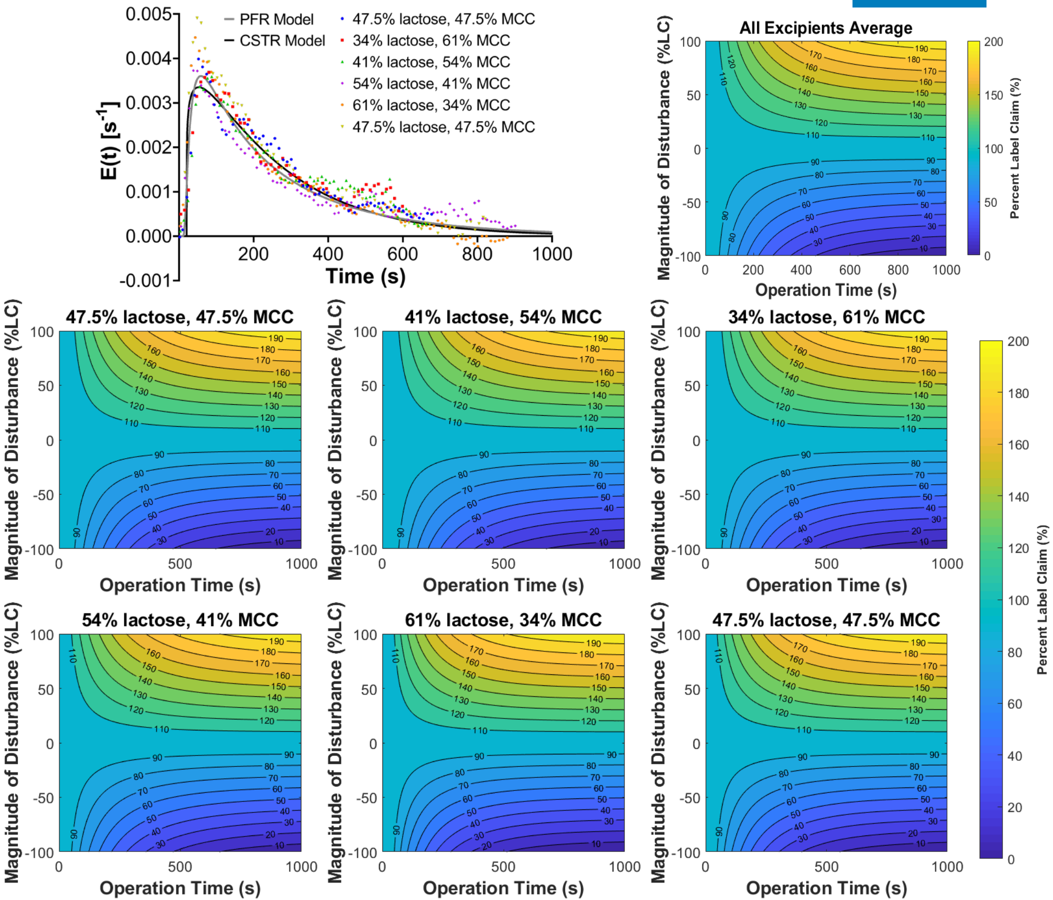
Effect of Bulk Material Properties on RTDs

- Is an overall fit encompassing data sets from all blending runs with varying excipient ratio an adequate fit for individual runs?
- Funnel plot of combined data fit similar to funnel plots of individual runs
  - Suggests overall fit may adequately represent RTD across range of excipient ratios
  - Safety buffers can be used to account for residual uncertainty depending on the application



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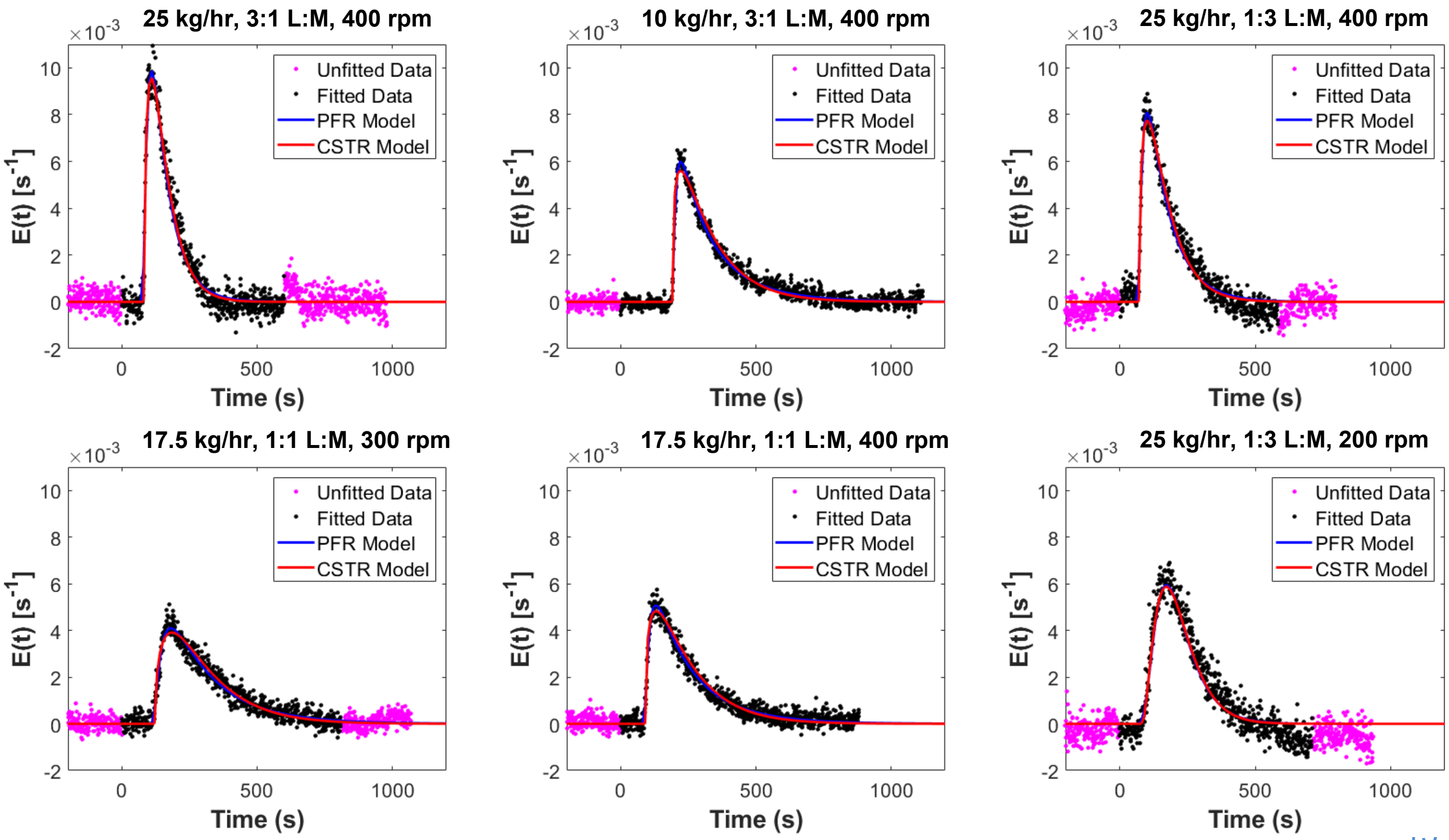
RTD Model Fitting

- Normalized API tracer concentration curves (RTDs) fitted to PFR and CSTR models
- Both models exhibited similar goodness of fit
  - Data prior to tracer insertion and after API feeder refills (magenta) excluded from model fitting



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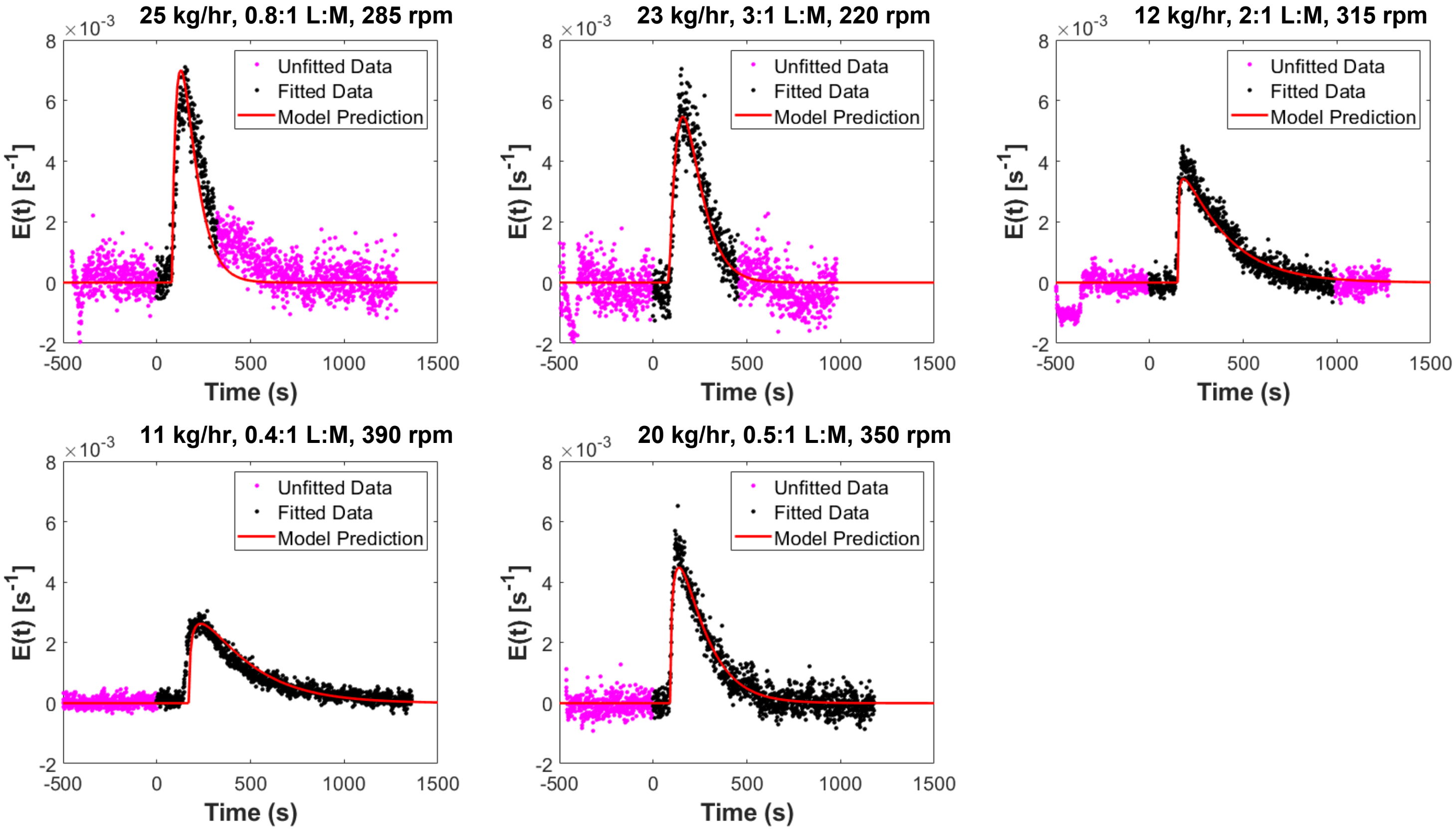
RTD Model Validation

- CSTR model used to predict RTD of external validation blending runs, projected over measured data
  - Data prior to tracer insertion and after API feeder refills (magenta) excluded from model fitting



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Concluding Thoughts

FDA

- Understanding how bulk material properties and process conditions affect the RTD of a process is critical for process understanding
  - Significant differences in RTDs were observed following changes in process parameters (e.g., blender speed, impeller configuration)
  - Slight differences in RTDs were observed following changes in bulk properties
- RTD models can enable real-time prediction of feeding material disturbances on blend and content uniformity
  - The level of understanding demonstrated should be commensurate with how the RTD models are used as part of the control strategy
  - RTD model assumptions should be justified with appropriate considerations for the limitations of the model

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