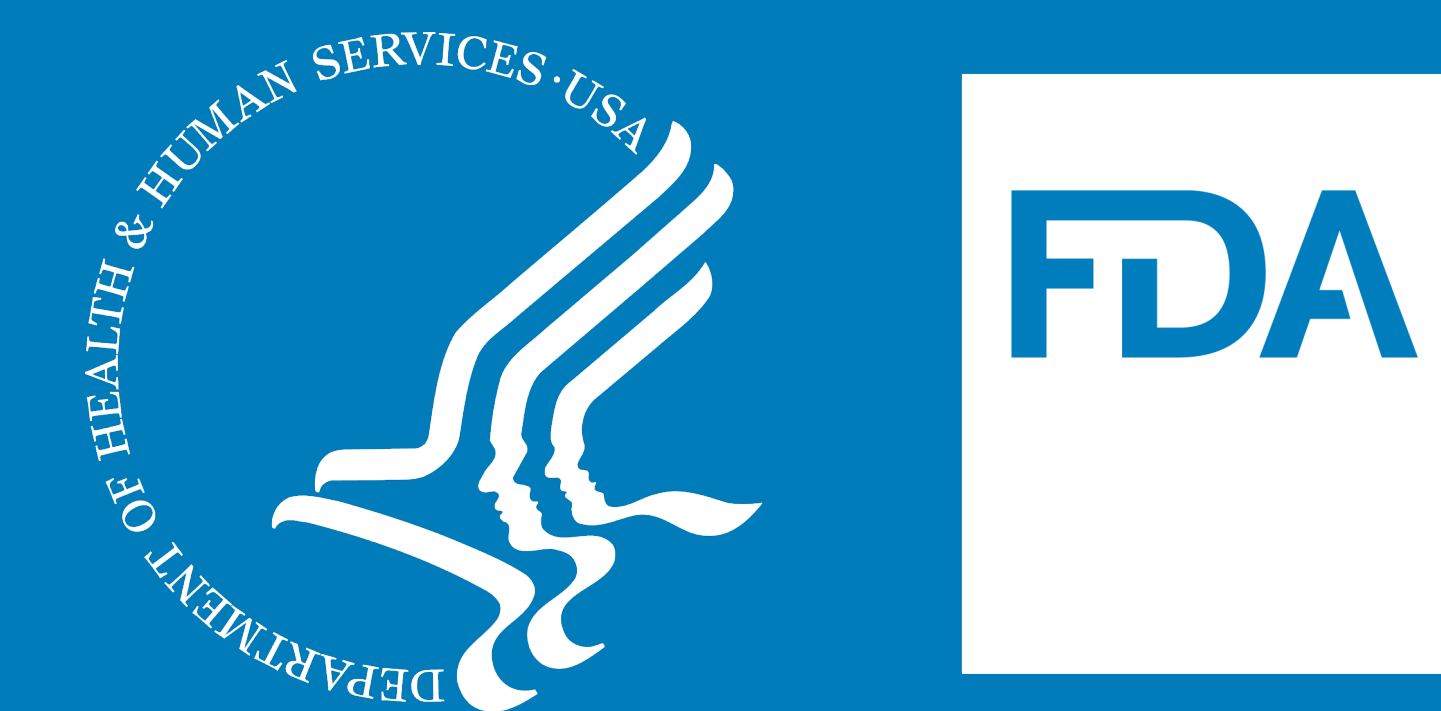


Predictive Residence Time Distribution Models for Continuous Powder Blending

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Objective

Predictive residence time distribution (RTD) models are developed and validated for commercial scale continuous powder blending at two different active pharmaceutical ingredient (API) loadings (5% and 30% w/w). The RTD models incorporated variation in bulk material properties, flow rate, and blender speed.

Background

Continuous manufacturing is an emerging technology with potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing. RTDs can be used to trace the flow and dispersion of material through a continuous process. Development of traceability algorithms using RTDs enables prediction of how disturbances propagate through a process, allowing for isolation/diversion of out-of-specification material. Given that RTD models can be used for feed-forward process control, they are considered medium-impact models. Sponsors have utilized different approaches for generating data on the effects of material properties and process parameters on the outputs of RTD models and the data is evaluated during the quality assessment. Improved understanding of the impact of material properties and process parameters on predictive RTD models will support future quality assessments and policy development on continuous manufacturing.

Equipment

- Three loss-in-weight feeders fed API and excipients into a continuous tubular blender containing a configurable shaft
- Near infrared (NIR) spectrometer was positioned below blender outlet to monitor blend composition in real time
- Powder dosing valve was used to maintain plug flow movement over NIR probe

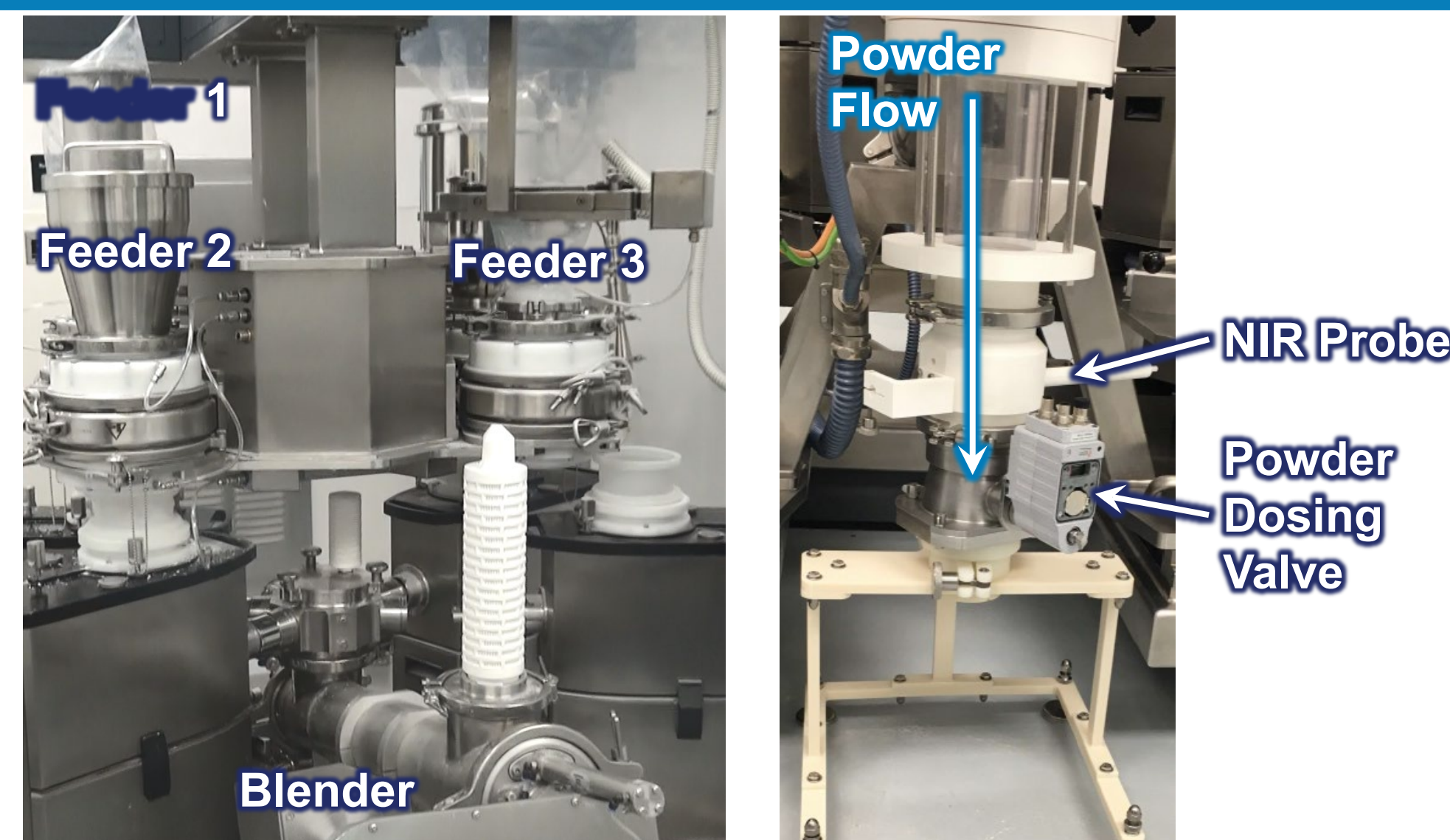


Figure 1. Continuous powder feeding and blending unit (left), PAT stack with NIR probe and powder dosing valve (right)

Data Collection

Offline NIR calibration models were established using the same powder chute/NIR probe assembly as the inline measurements. NIR spectra were collected approximately once per second during blending runs, and API content of the exiting blends was estimated based on the appropriate NIR calibration model. NIR model accuracy was validated against offline API content assessment of blend samples via HPLC.

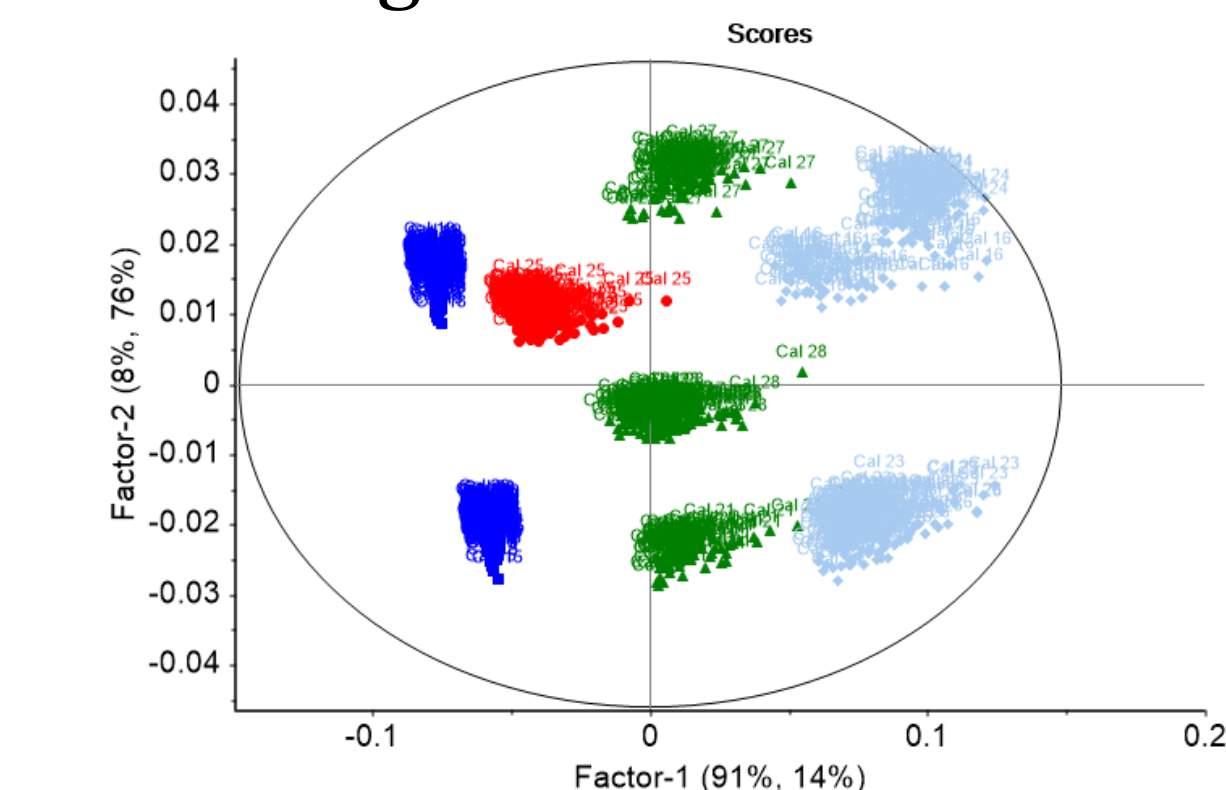


Figure 2. Scores plot for one of the partial least squares regression models predicting API content of blends from NIR signal

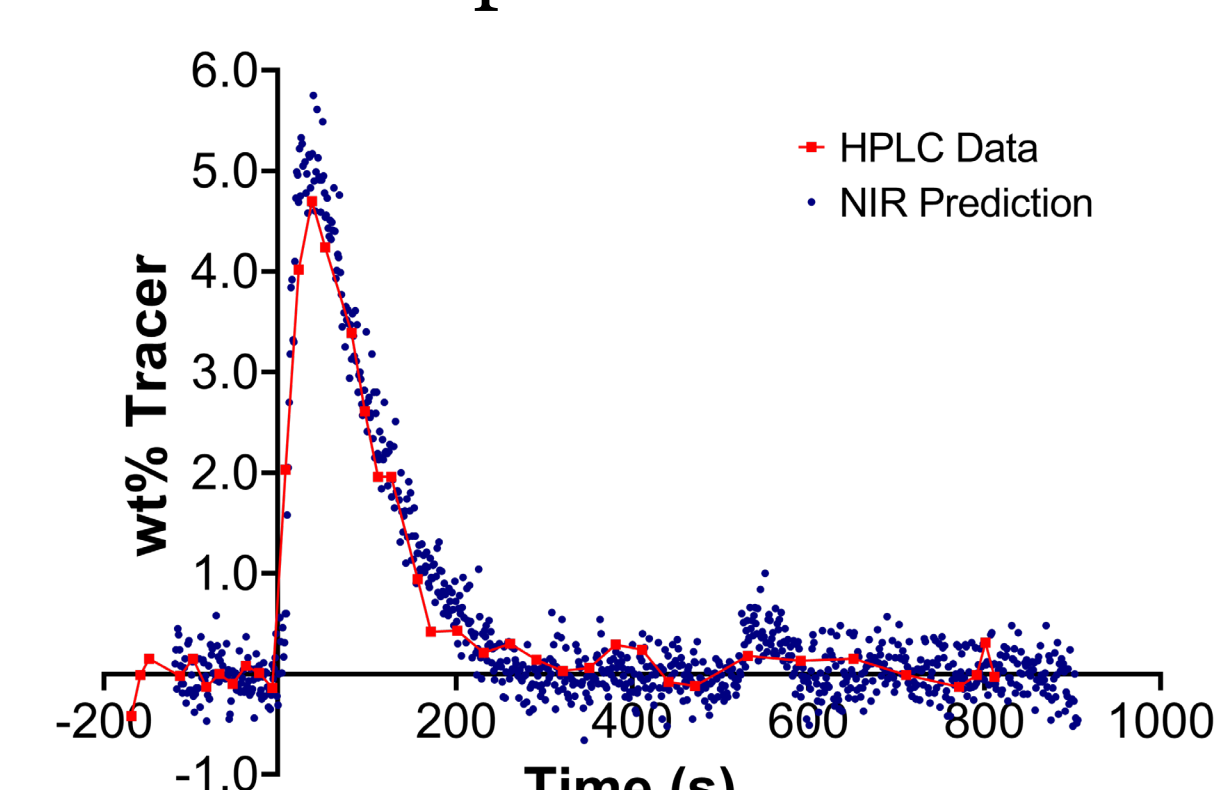


Figure 3. API content of exiting blend as a function of time based on offline experimental data (HPLC, red) and NIR method prediction (blue)

Baseline Conditions

Table 1. Base formulations of powder blend and component material properties

Material	Function	wt% (low API)	wt% (high API)	d_{50} (μm)	CBD* (g/mL)
Semi-fine Acetaminophen (APAP)	API	5.0	30.0	21.72	0.348
Lactose Monohydrate	Filler	47.5	35.0	34.39	0.578
Microcrystalline Cellulose (MCC) 102	Filler	47.5	35.0	126.35	0.353

*CBD: Conditioned bulk density

Table 2. Experimental parameter ranges for continuous blending RTD model development

Baseline API Content (wt%)	Total Flow Rate (kg/hr)	Blender Shaft Speed (rpm)	Lactose-to-MCC Ratio (L:M)
5.0	10.0 – 25.0	200 – 400	3:1, 1:1, 1:3
30.0	10.0 – 25.0	225 – 400	3:1, 1:1, 1:3

RTD Model and Metrics

Residence Time Distribution (RTD): $E(t) = \frac{C_{out}(t) - C_0}{\int_0^{\infty} [C_{out}(t) - C_0] dt}$

Mean Residence Time (MRT): $MRT = \tau = \int_0^{\infty} tE(t) dt$

Mean Centered Variance (MCV): $\sigma^2 = \int_0^{\infty} \frac{(t - \tau)^2 E(t)}{\tau^2} dt$

Tanks-in-Series (CSTR) Model: $E(t) = \frac{N-1}{\theta} \frac{t^{N-1}}{\Gamma(N)} \exp[-Nt/\theta]$, $t > t_{lag}$

t = Time
 C_{out} = Exit API concentration
 C_0 = Initial API concentration
 t_{lag} = Lag time
 N = Theoretical number of CSTRs
 Γ = Gamma function
 θ = Dimensionless time: $(\theta = \frac{t - t_{lag}}{\tau})$

RTD Model for 5% API Blends

- Normalized API tracer concentration curves (RTDs) for 5 wt% APAP blending runs fitted to CSTR model

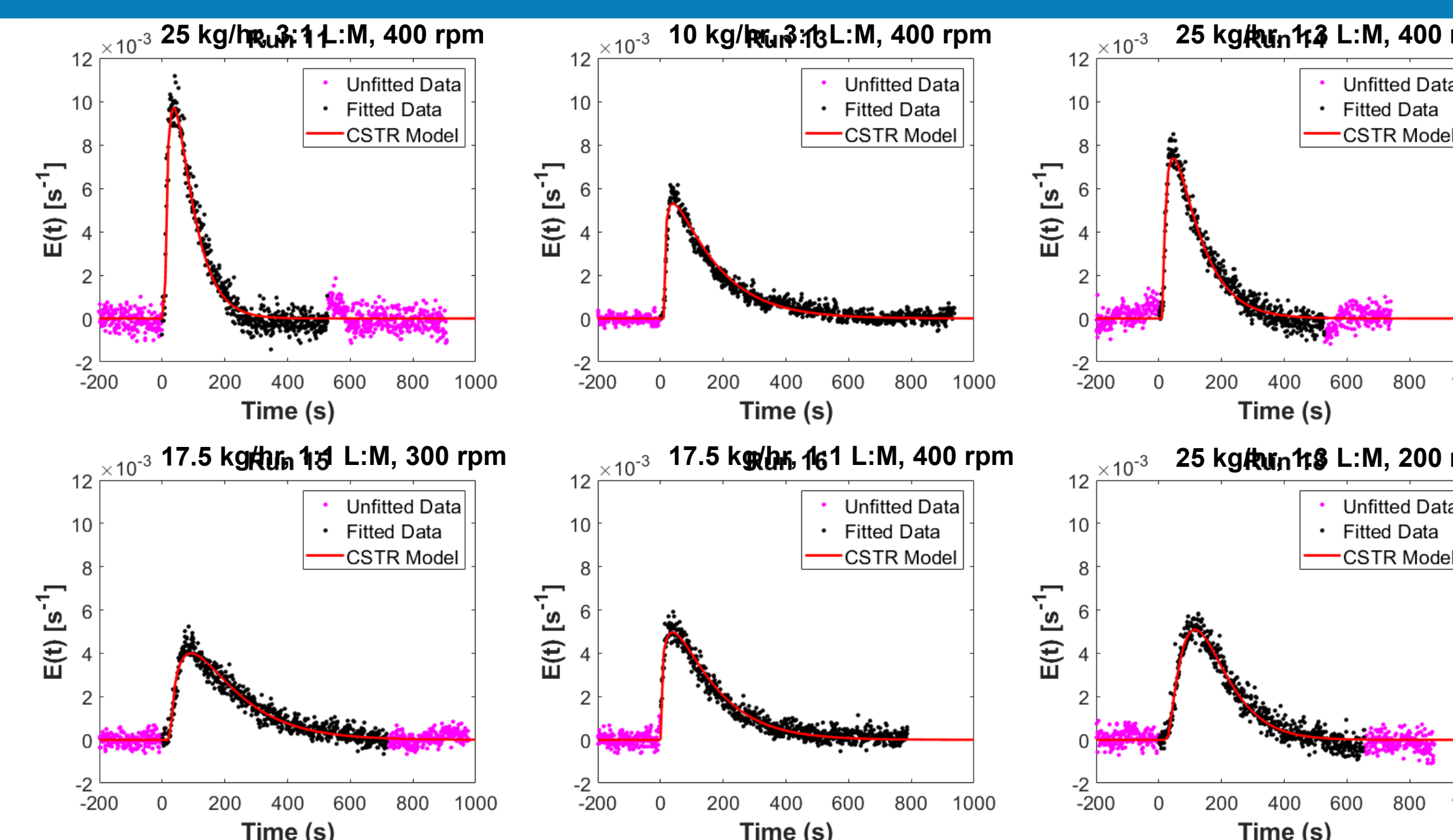


Figure 4. Sample of RTDs used to construct RTD model for 5 wt% API blends and their respective CSTR model fits

- CSTR model exhibited strong fit of blender RTDs

- RTD model used to predict RTD of new 5 wt% API blending runs, projected over measured data

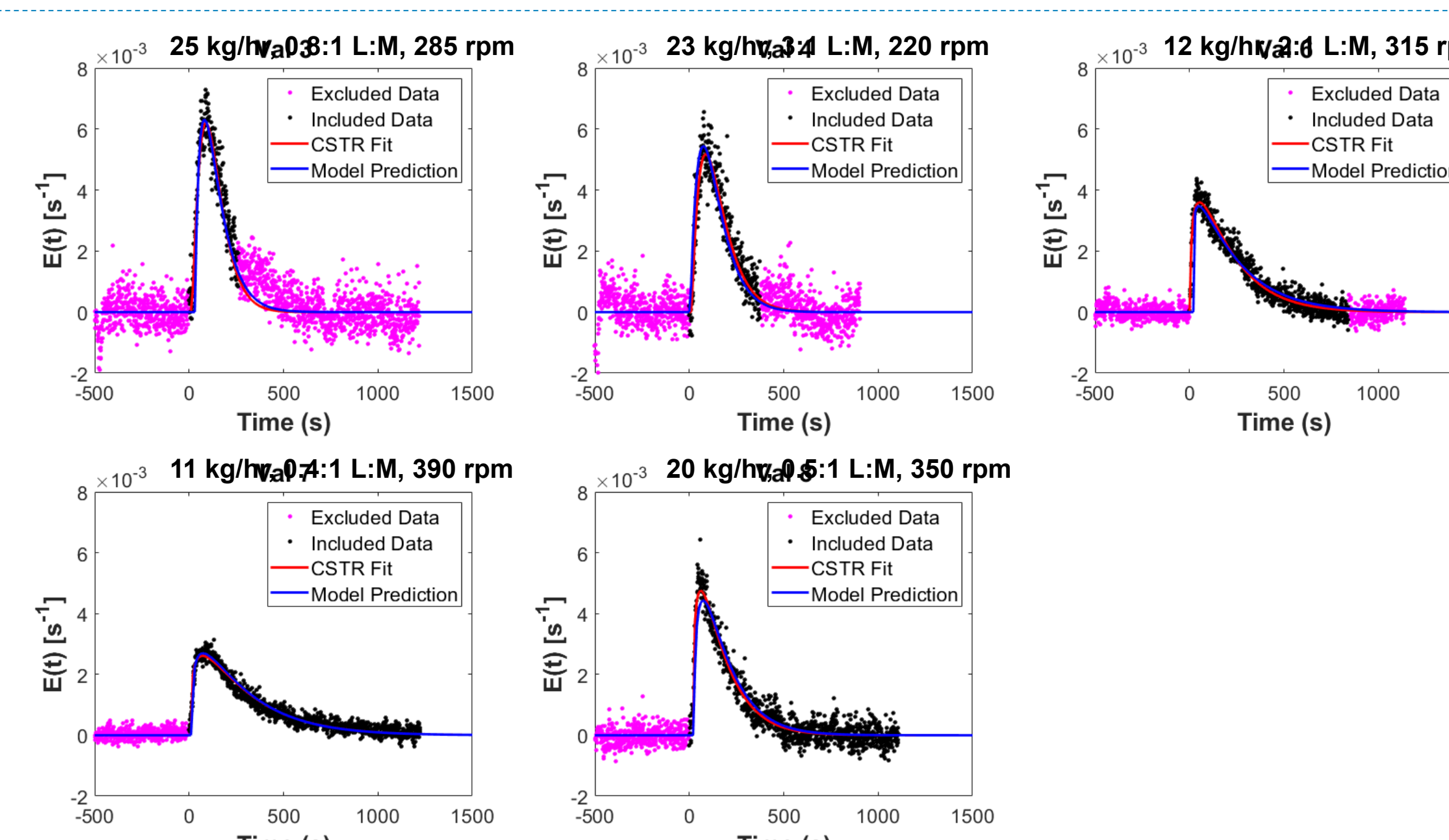


Figure 5. Sample of RTDs used to validate RTD model for 5 wt% API blends with superimposed RTD model predictions

- Model predicted RTDs of external validation runs reasonably well
- RTD peak location, height, and width were all predicted with good accuracy

RTD Model for 30% API Blends

- Normalized API tracer concentration curves (RTDs) for 30 wt% APAP blending runs fitted to CSTR model
- CSTR model exhibited reasonable fit of blender RTDs
 - Greater variation in API concentration estimates via NIR than observed in 5% API blending runs

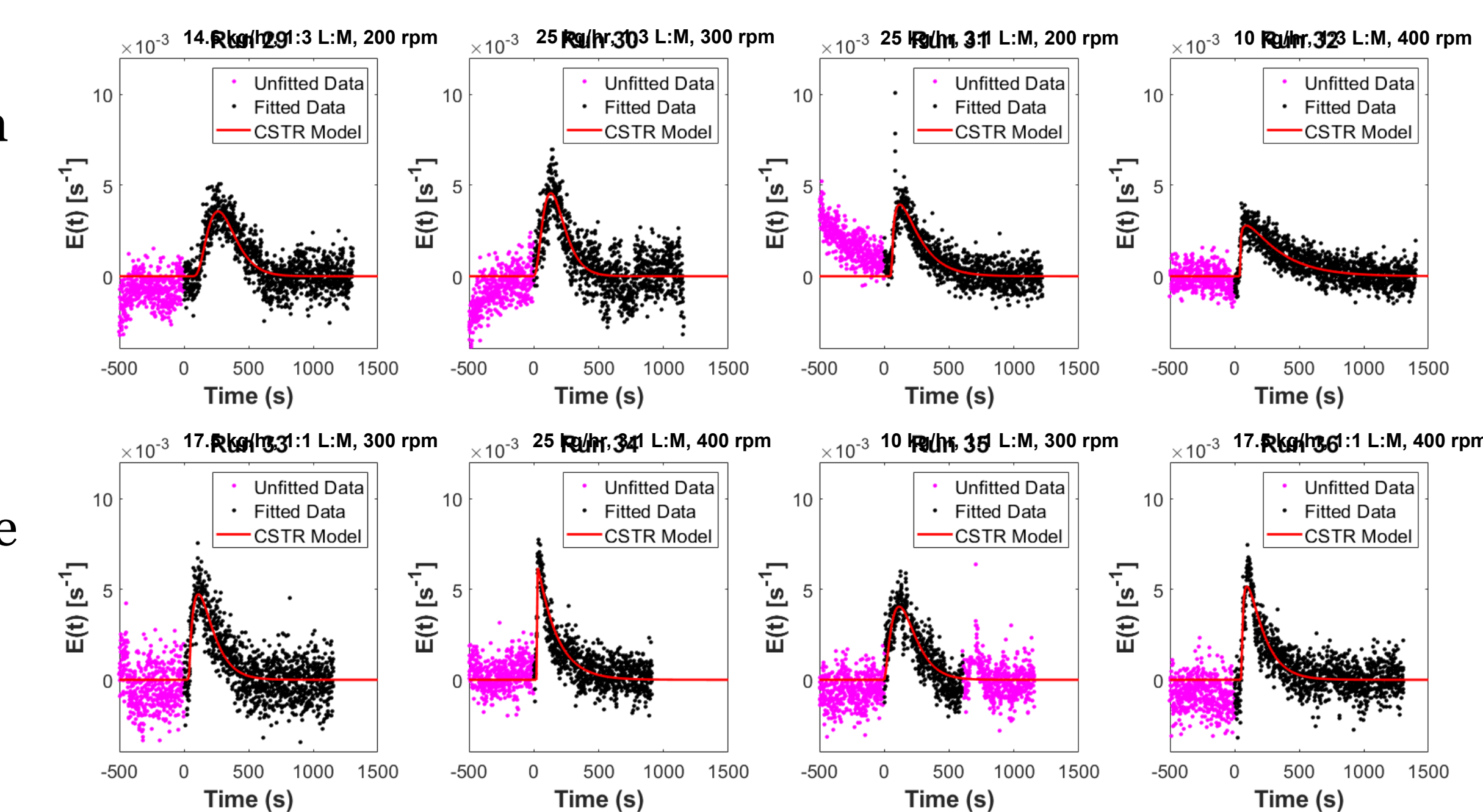


Figure 6. Sample of RTDs used to construct RTD model for 30 wt% API blends and their respective CSTR model fits

- RTD model used to predict RTD of new 30 wt% API blending runs, projected over measured data
- Weaker predictive performance for 30 wt% API RTDs than for 5 wt% API RTDs
 - Greater variation in API concentration estimates via NIR
 - Less stability in baselines used to normalize RTDs

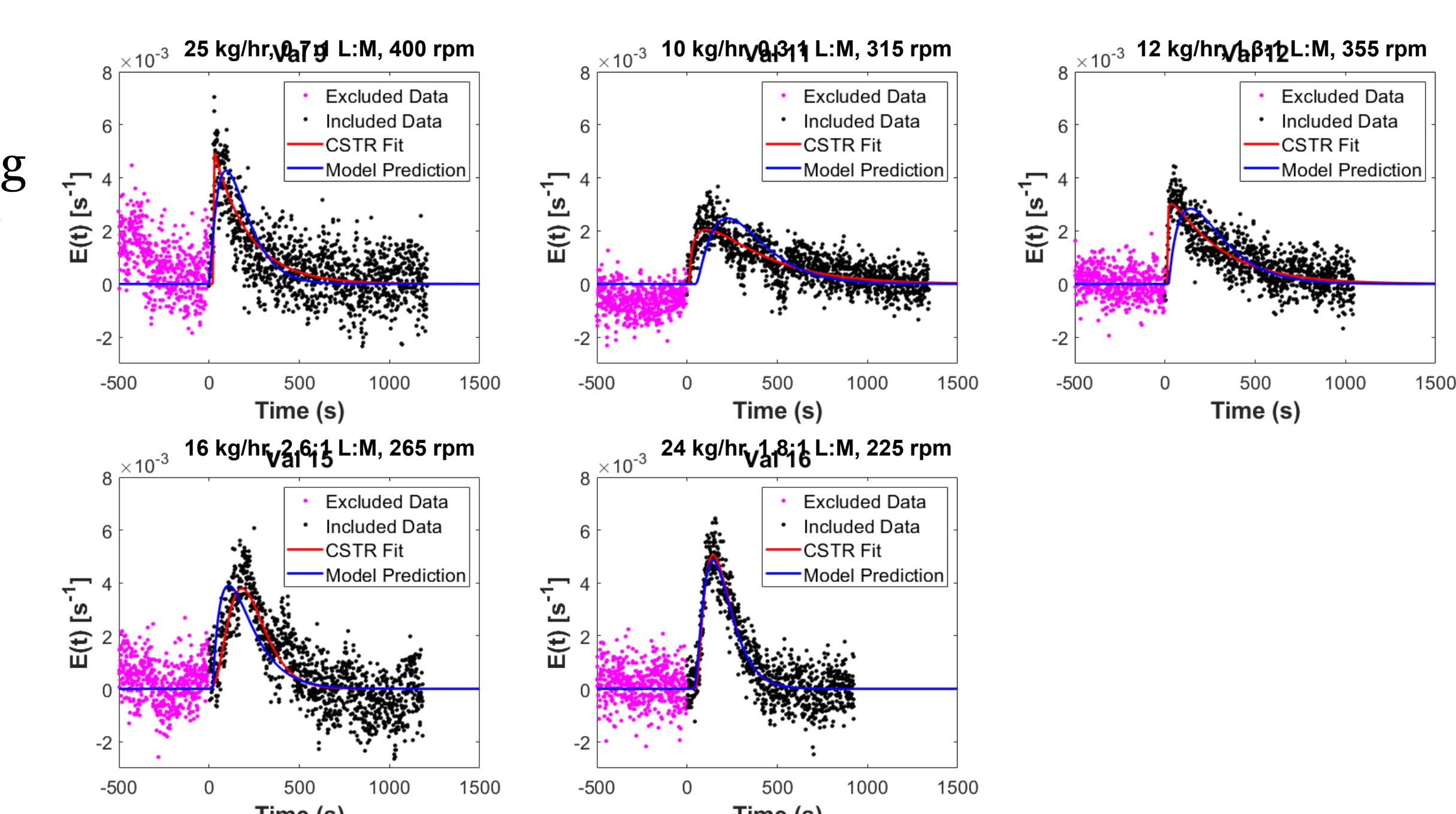


Figure 7. Sample of RTDs used to validate RTD model for 30 wt% API blends with superimposed RTD model predictions

Conclusions

- Understanding how bulk material properties and process parameters affect the RTD of a continuous process is critical for process understanding.
- The level of understanding demonstrated in regulatory submissions that make use of RTD models should be commensurate with how the RTD is being used as part of the control strategy.
- RTD model assumptions should be justified with appropriate considerations for the limitations of the model.
- The quantification of how material properties and process parameters affect RTDs further the Agency's understanding of the continuous powder blending process, as well as the techniques used to monitor and control it.
- Results from this study are being utilized to inform regulatory decisions regarding use of RTD models for control of powder flow processes, as well as policy development and reviewer training for continuous manufacturing applications.

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