Development and Utilization of Process Modeling and Simulations for Supporting Quality Risk Assessment and Control of Continuous Pharmaceutical Manufacturing

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Abstract

- Flowsheet modeling of a continuous direct tablet compression process is exploited to identify process parameters and material attributes that affect critical quality attributes of the tablet.
- Validated model is used for material traceability and for the assessment of in-process control strategies for the feeders.
- The simulation results show that the employed modeling approach facilitates risk-based assessment of the continuous line by promoting our understanding of the CM process.

Introduction

- FDA has recently approved drug applications which include CM processes. Market demand and the benefits of CM are shifting the pharmaceutical industry towards implementing more CM processes.
- Process models can aid process design by estimating the impact of process and equipment parameters, and material attributes on product attributes.
- Process models can be used as a quantitate tool for the risk evaluation and material traceability in CM processes. Process models can provide useful data for process development, validation and can be incorporated as a component of the control strategy to ensure product quality.

Method

- A common CDC process including raw material feeding, blending, and tablet compression is considered, as shown in Figure 1 (left).

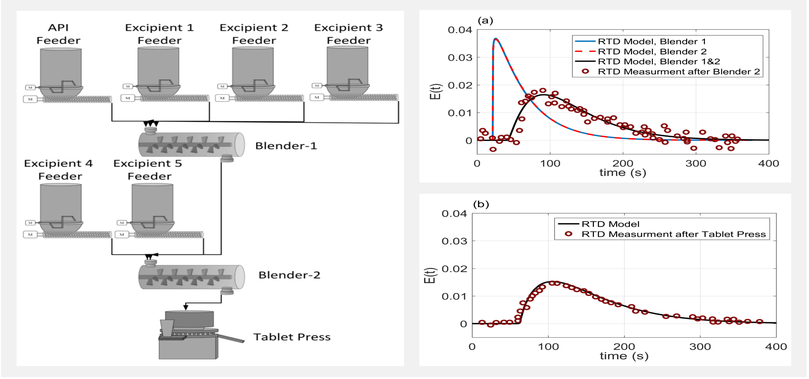

Figure 1. (left) Schematic of a typical process flow diagram for CDC tablet, and (right) Comparison of experimental and predicted RTD models at (a) discharge of the blender 2, (b) after the tablet press

- A combination of mechanistic and empirical models were developed and validated for the process unit operations and were used to predict tablet quality attributes (refer to [1 -2] for more detail).
- Sensitivity analysis (using Morris and Sobol methods) was used to identify the process parameters and material attributes that are critical to product quality.

Results and Discussion

- The results of sensitivity analysis (Figure 2) suggest that the API and the excipients density, their flowrates, the blender's rpm, tablet die fill depth, and main compression force are the most significant factors that impact process operability and tablet quality.

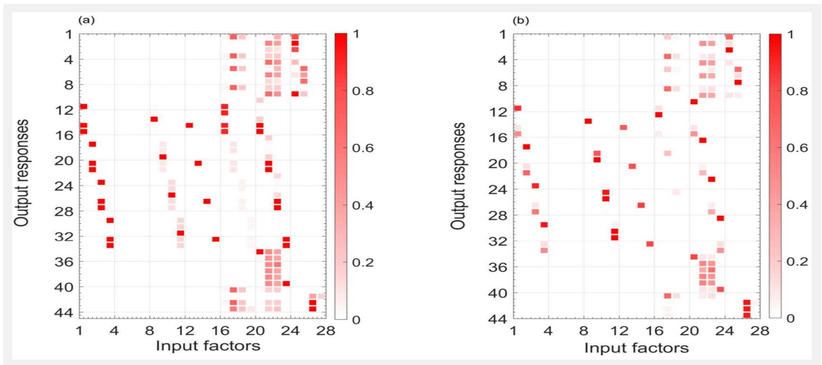

Figure 2. Intensity plots representing steady-state sensitivity analyses that capture the effects of input factors on the output responses for (a) Morris and (b) Sobol Method; good agreement observed between both methods

- RTD model is used to capture the effects of flow disturbances in the feeders on the API concentration after the tablet press.
- Figure 3 suggests that it is crucial to consider the feeders interactions on the tablet composition and design a flow rate control strategy that ensures product quality. These funnel plots are very useful in predicting time to accept/reject the blend/tablets when upstream disturbances in the feeders occur.
- The %target composition of each component at the feed frame versus the duration of flow disturbance in the feeder for the same component is shown in Figure 4.
- IPC %target composition alarm limits for the feed frame are set to complement the feeder alarm. Providing flexibility in setting feeder alarm limits to increase process robustness and minimize impact on product quality.

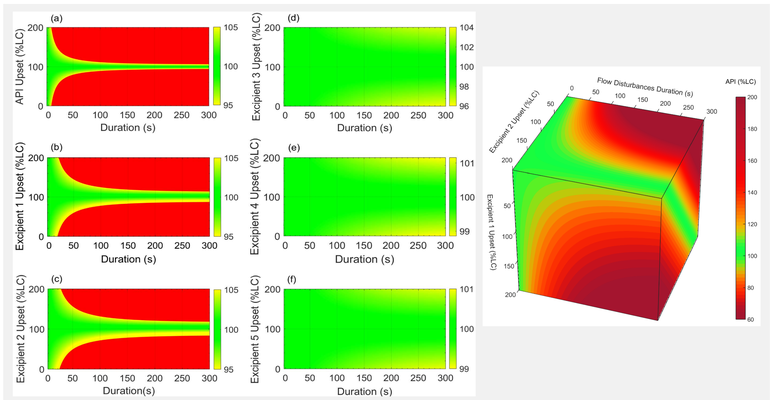

Figure 3. Impact of (left) feeding disturbances on the final concentration of the API in the tablet as a function of time, and (right) simultaneous disturbance in the flowrate of feeders 1 and 2 on the API in the tablet as a function of time.

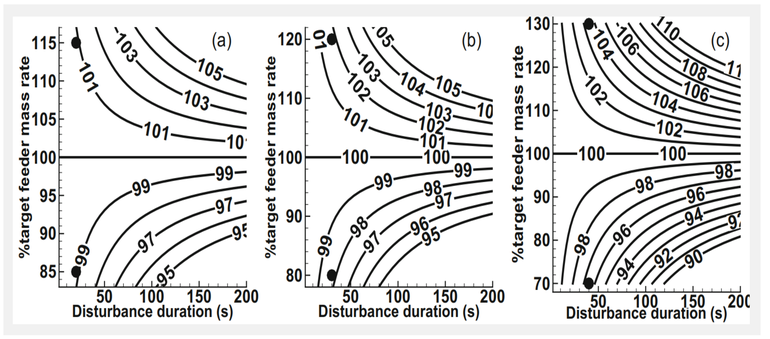

Figure 4. (a) Predicted peak concentrations in the feed frame for various feeder disturbances: API feeder, and (b) excipient 1 and 2 feeders, and (c) excipient 3 and 4 feeders. (Black circle represents the individual feeders IPC limit)

Conclusion

- Validated flowsheet models can provide accurate predictions of the impact of process parameters and material attributes on critical quality attributes of drug products produced via continuous pharmaceutical manufacturing
- The developed process modeling approaches have been used in the regulatory assessment of drug applications employing CDC processes by identifying high risk areas and facilitating the evaluation of risk mitigation strategies.

References

1-Tian et al. Computers & Chemical Engineering 129 (2019): 106508.
2-Tian et al. AAPS PharmSciTech 22.1 (2021): 1-10.