Assessing Residence Time Distributions and Hold-up Mass in Continuous Powder Blending using Discrete Element Method

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Introduction

Continuous manufacturing is recognized by FDA/ICH as a candidate technology for pharmaceutical modernization[1,2]. It offers several advantages over batch processes, such as smaller footprint, less operation steps, and adaptable to real-time process monitoring and control. Residence time distribution (RTD) is often used to describe the transport of materials in continuous processes. They are traditionally measured by pulse or step experiments. This work aims to investigate an alternative approach, which is discrete element method (DEM) simulations, to obtain RTDs for a continuous blade blender.

Mathematical Model

The discrete element method is a numerical technique that is used to predict the behaviors of collision dominated particle flows. It tracks each particle in a process and models all collisions between particles and between particles and boundaries. The particles can slightly overlap, and the extent of the overlap is used in conjunction with a contact force law to give instantaneous forces from knowledge of the current positions, orientations, velocities, and spins of the particles. The contact force law is resolved into normal ($\mathbf{f}_n$) and tangential ($\mathbf{f}_t$) components.

$$\mathbf{f}_n = \frac{4E}{3R}a^3\mathbf{n} - 4\sqrt{\pi\gamma E}\,a^{\frac{3}{2}}\,\mathbf{n} - 2\sqrt{\frac{5}{6}}\beta\sqrt{S_n m}\,\mathbf{v}_n$$

$$\mathbf{f}_t = -S_t\delta_t\mathbf{t} - 2\sqrt{\frac{5}{6}}\beta\sqrt{S_t m}\,\mathbf{v}_t$$

$$\frac{a^2}{R} - \sqrt{\frac{4\pi\gamma a}{E}} - \delta_n = 0$$

$$\beta = -\frac{\ln e}{\sqrt{\ln^2(e) + \pi^2}}$$

$$S_n = 2E\sqrt{R\delta_n}$$

$$S_t = 8G\sqrt{R\delta_n}$$

E Young's modulus
G Shear modulus
e Coefficient of restitution
γ Surface energy
m Particle mass
R Particle radius
S_n , S_t Stiffness
δ_n , δ_t Overlap

The blender DEM model consisted of an inlet hopper, a cylindrical container, and a rotational shaft integrated with 28 impeller elements. Each impeller element had two blades that were located on opposite sides around the shaft axis. Two types of the elements were used: transport element and mixing element. The transport element had two 45° blades. The mixing element had a 45° blade and a 0° blade. The angle was relative to axial direction.

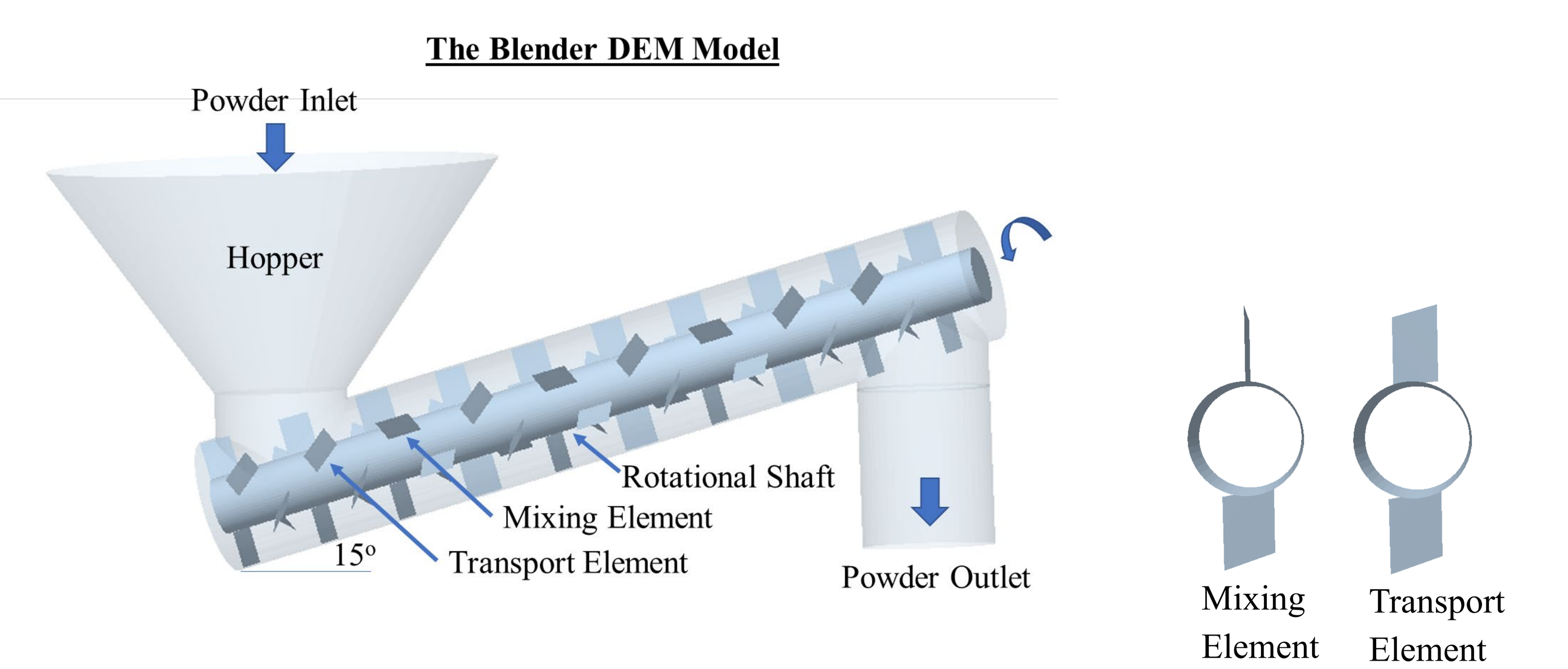

Fig 1. Illustration of the blender DEM model with enlarged views of the mixing and transport elements.

Model Validation

The validity of the blender DEM model was assessed using measured residence time distributions (Runs 1-14) for a wide range of operating conditions after modeling calibration (Run 0). The simulation results showed good agreements with the experiments.

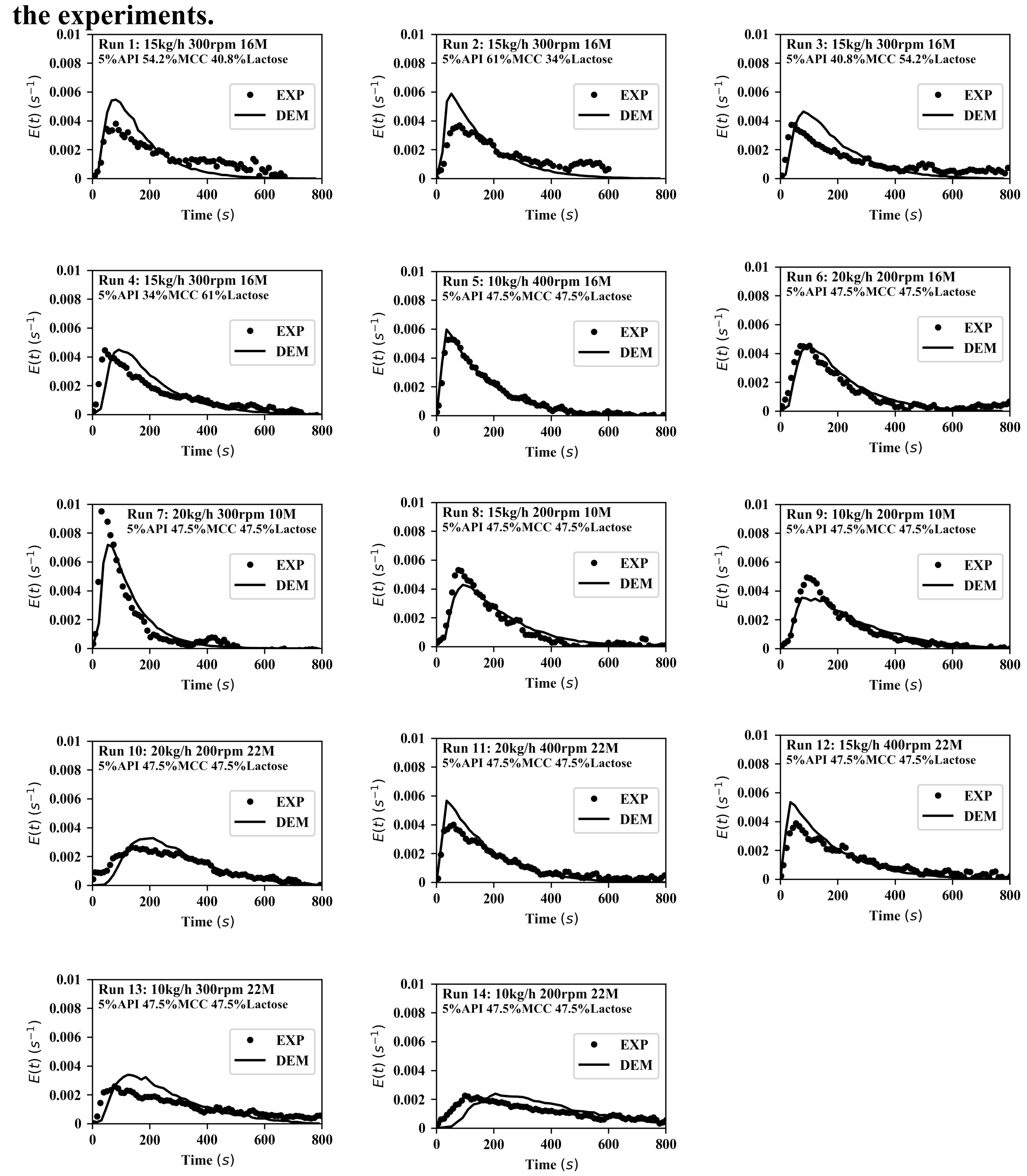

Fig 2. Comparison of the residence time distributions between simulations and experimental measurements.

Effect of Mass Flow Rate

The mass flow rate influences both the mean residence time and the spread of the residence time distribution. As the mass flow rate increased from 10kg/h to 30kg/h, the mean residence time decreased by 44%, and the spread of the residence time distribution also increased. Moreover, the hold-up mass increased linearly with increasing the mass flow rate.

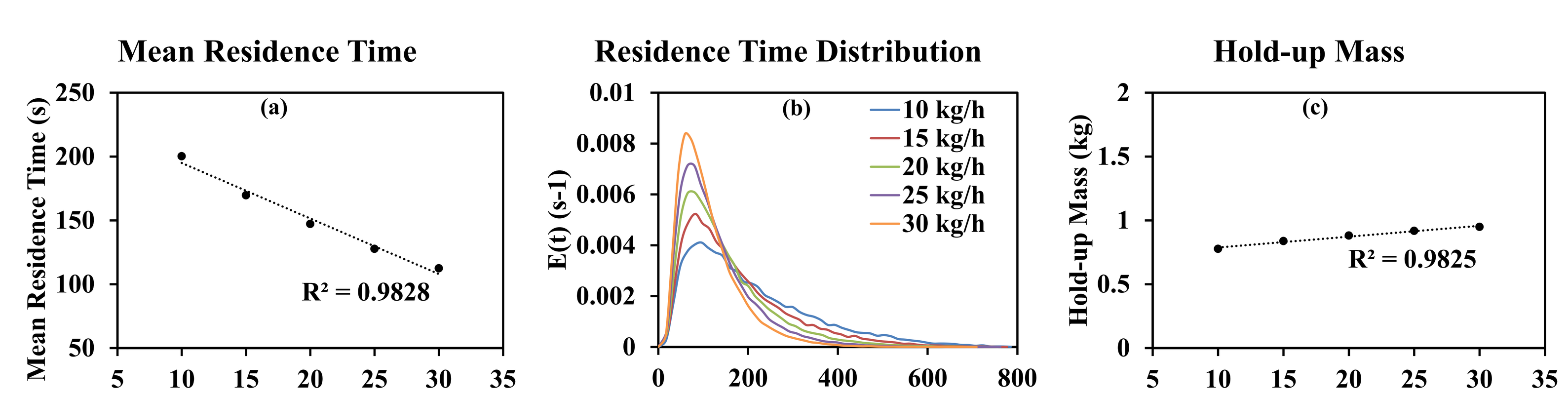

Fig 3. Effect of mass flow rate on the particle residence time and the blender hold-up mass. Process conditions: 300rpm, 16M, 5%API, 47.5%MCC, 47.5%Lactose

Effect of Blender Element Pattern

The effect of the number of mixing elements were studied between 10 and 22 mixing elements. Both the mean residence time and the hold-up mass increased with increasing the number of mixing elements. The spread of the residence distribution also increased slightly with increasing the number of mixing elements.

Table 1. Blender element pattern ("T": transport element; "M": mixing element)

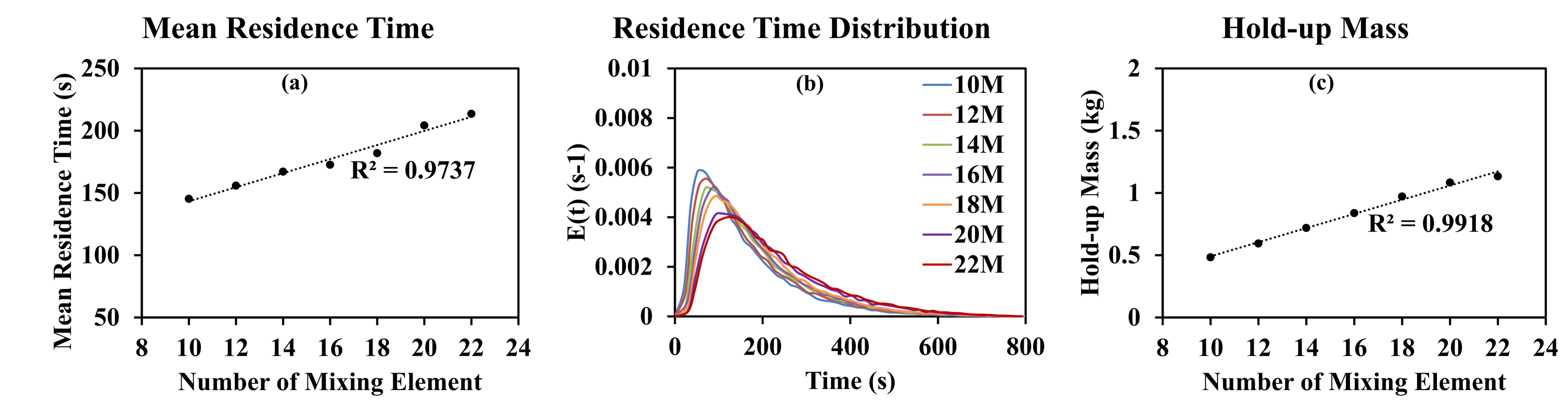

Fig 4. Effect of the number of mixing elements on the particle residence time and the blender hold-up mass. Process conditions: 15kg/h, 300rpm, 5%API, 47.5%MCC, 47.5%Lactose

Effect of Blender Speed

The blender speed had significant impacts on the particle residence time and the blender hold-up mass. The mean residence time reduced by 57% and the hold-up mass reduced by 85% when the blender speed increased from 200rpm to 400rpm. Meanwhile, the residence time distribution shifted to smaller times and became less dispersed with increasing the blender speed.

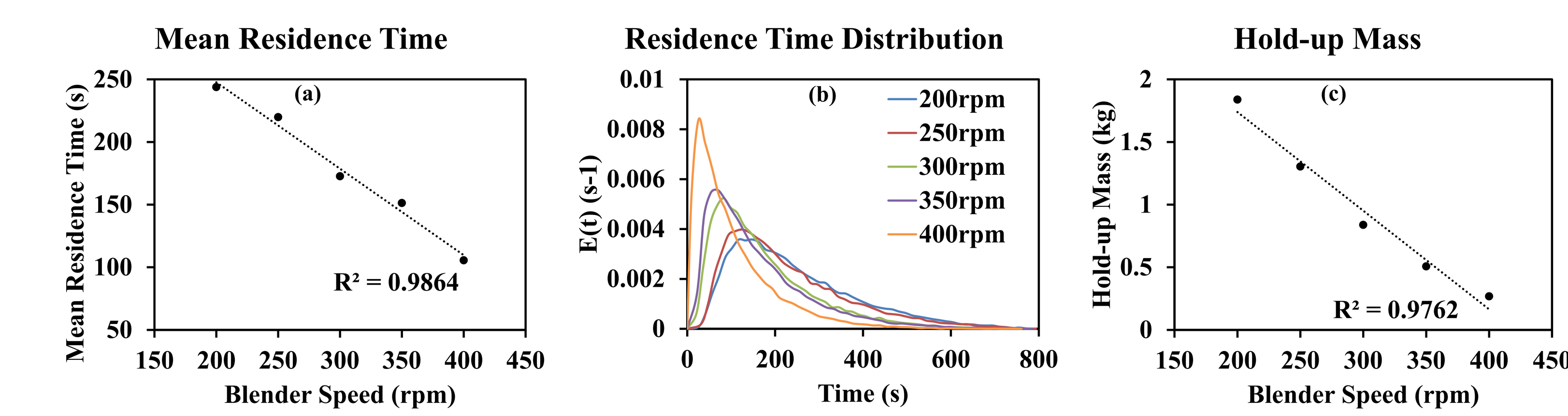

Fig 5. Effect of the blender speed on the particle residence time and the blender hold-up mass. Process conditions: 15kg/h, 16M, 5%API, 47.5%MCC, 47.5%Lactose

Conclusion

- A DEM model was developed and validated against the RTD experiments.
- The effects of the mass flow rate, the blender element pattern, and the blender speed on the residence time distribution and the hold-up mass were then studied via DEM with One-at-a-time virtual DOE.
- The good linearity between the particle residence time and the blending parameters suggests that the blender is well designed for scale-up.
- High-fidelity DEM can be used to evaluate RTD-based control strategies.

Reference:
1. *Q13 Continuous Manufacturing of Drug Substances and Drug Products by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.* 2021.
2. *Quality Considerations for Continuous Manufacturing Guidance for Industry by U.S. Food and Drug Administration.* 2019.