QbD based model development for continuous pharmaceutical manufacturing

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Introduction

Plant wide models for continuous pharmaceutical manufacturing facilitate process optimization. This Quality by Design (QbD) based approach takes regulatory requirements into account and leads to higher process understanding, see [1]-[3]. Simulations can reduce time and cost intensive experimental runs, shorten time to market and hence increase profit margin while assuring product quality.

Methods

Blending was chosen as exemplary unit operation to demonstrate QbD based model development. Source code was written in Matlab/Simulink (The MathWorks, Inc., Natick, Massachusetts, US) and gSOLIDS (Process Systems Enterprise Limited, London, UK).
First, the critical material attributes (CMAs), critical quality attributes (CQAs) and critical process parameters (CPPs) were identified. The blend homogeneity is essential for content uniformity of tablets and it is the only quality determining parameter in this unit operation. Residence time distribution (RTD) model was chosen because of simplicity and low calculation time. This approach allows also particle tracking through the process.

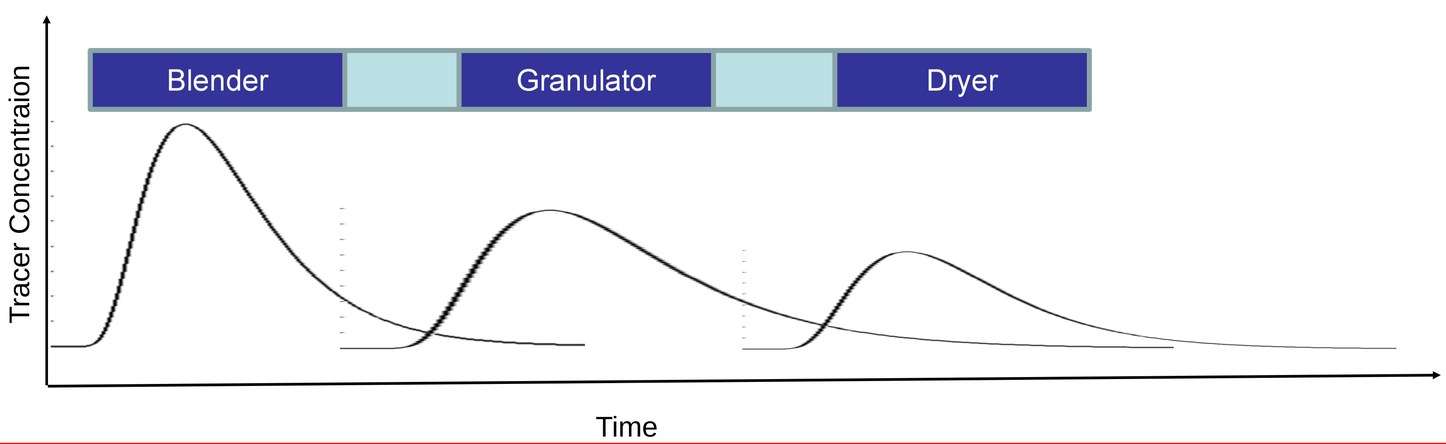

Fig.1: Tracer concentration over time after different downstream unit operations which can be used for particle tracking.

Modeling of Residence Time Distribution for a Continuous Blender

$$\frac{\partial C}{\partial \theta} + \frac{\partial C}{\partial \xi} = \frac{1}{Pe}\frac{\partial^2 C}{\partial \xi^2}$$

$$C(\xi,\theta) = \frac{C_0 Pe^{0.5}}{(4\pi\theta)^{0.5}}\, e^{-\frac{Pe(\xi-\theta)^2}{4\theta}}$$

$\theta = \frac{t-t_0}{\tau}$, $\xi = \frac{z}{l}$, $\xi = 1$ for RTD at blender outlet

$$P(s) = \frac{Y(s)}{U(s)} = \frac{1}{(1+sT_1)} \cdot \frac{1}{(1+sT_2)} \cdot \frac{1}{(1+sT_3)} \cdot e^{-sT_t}$$

The solution to the dimensionless Fokker-Planck equation (convection diffusion equation) $C(\xi,\theta)$ [4] was approximated by a linear transfer function $P(s)$ as output $Y(s)$ divided by input $U(s)$.

- θ = dimensionless time, with t_0 as impulse duration and τ as mean residence time
- C_0 = start concentration
- C = concentration
- z = spatial coordinate in axial direction
- t = time
- D = diffusion coefficient
- l = length of blender
- v = velocity
- ξ = dimensionles spatial coordinate in axial direction
- T_1, T_2, T_3 = Time constants and T_t = delay time

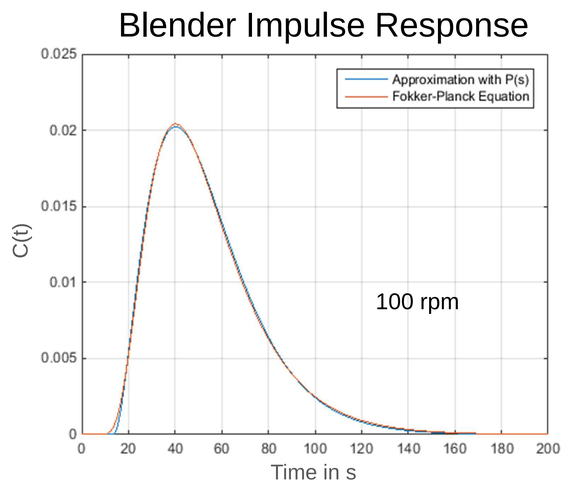

Fig.2: Comparison of $C(\xi,\theta)$ and the impuls response of $P(s)$.

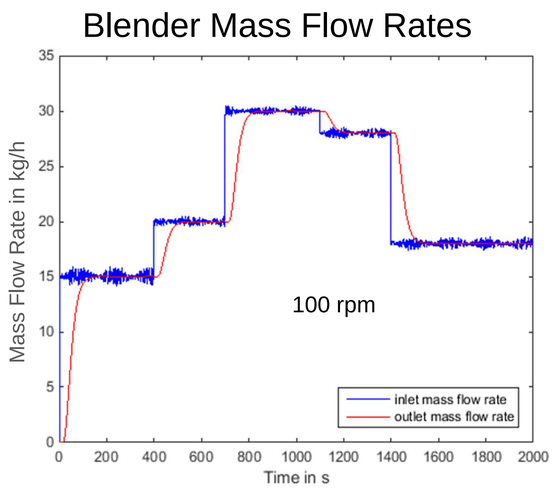

Fig.3: Inlet mass flow rate (blue) and outlet mass flow rate (red) of the blender

Results and Outlook

Residence time distribution models are suitable for prediction of relative standard deviation of the concentration at the outlet of the blender. Further, RTD provides information about the probability of a particle to stay in the corresponding unit for a certain time period. This probability density function can be used to calculate the location of a particle, fed at a certain time with a certain probability. This offers the opportunity for implementation of particle tracking to reject smaller amounts of material in case of malfunctions.

References

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