Control Strategy design of a Continuous Direct Compression Process for Oral Solids Dosages using Resident Time Distribution Studies

Author: Elvin O. Almodovar Garcia

Advisor: Rafael Nieves Castro, PharmD,

Department: Industrial Engineering Department

Abstract

In a continuous process any deviation from the intended process parameters can cause an unreliable product and economical losses. Residence time is a measure of how much time any given material or combination of materials spend inside a unit of a system. RTD studies for continuous manufacturing (CM) processes are used to determine the individual residence time of processing units within the system at given process conditions and equipment configuration. The RTD information can be used for material traceability, control strategy, for evaluating mixing performance, and to determine the blender noise filtering capability for the feeders' mass flow variations. In this study, a reject and accept control strategy was defined based on Residence Time Distribution studies.

Introduction

Continuous Manufacturing (CM) process technology is well-known and frequently used in the materials and food industry. In a continuous process any deviation from the intended process parameters can cause an unreliable product and economical losses. The project presented here focused on studying a real continuous manufacturing line to develop an efficient way to control the process using Residence Time Distribution to maintain the critical attributes of the process. A reject and accept strategy will be defined based on Residence Time Distribution studies.

Background

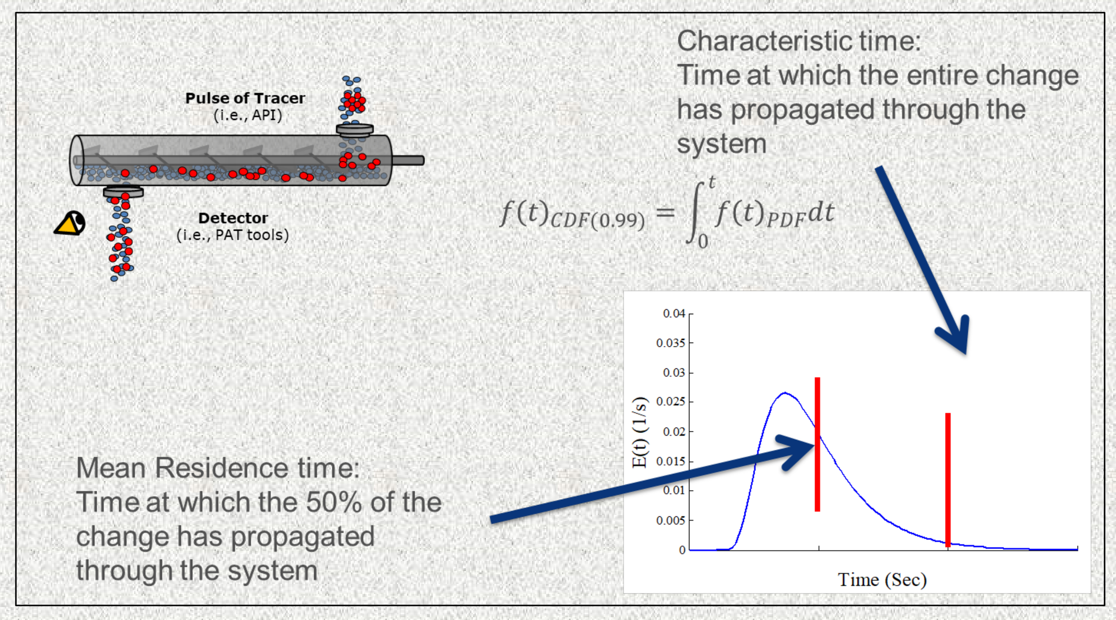
RTD studies for continuous manufacturing (CM) processes are used to determine the individual residence time of processing units within the system or for the system at given process conditions. The time that materials stay inside a continuous flow system is described in a quantitative manner by the residence time distribution function, E(T). The RTD function is defined as:

$$E(t) = \frac{c(t)}{\int_0^\infty c(t)dt} \qquad (1)$$

$$\tau = \int_0^\infty tE(t)dt \qquad (2) \qquad \sigma^2 = \int_0^\infty (t-\tau)^2 E(t)dt \qquad (3)$$

The Mean Residence Time (MRT) is the average time the tracer material stays in the system of interest. The Mean Centered Variance (MCV) is an indication of the spread of the distribution; the greater the magnitude of MCV, the greater a distribution's spread will be.

Figure 1 RTD Parameters



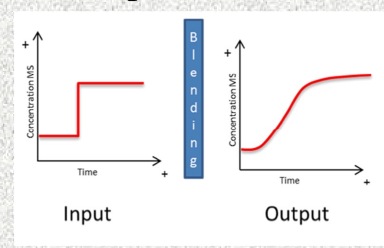
Methodology

The RTD of a continuous flow system can be determined by performing a step change experiment. A screening design at the extreme levels was executed to determine the space where we can expect our Residence Time distribution.

Table 1 Factors Levels

Run ID	Throughput	Blender Speed
1	-1	-1
2	0	0
3	1	1

Figure 2 Experiment In and Out



Step change experiments were performed modifying the composition of the API in 10 percent increase and decrease. Refer to Table 2 below for a list of materials

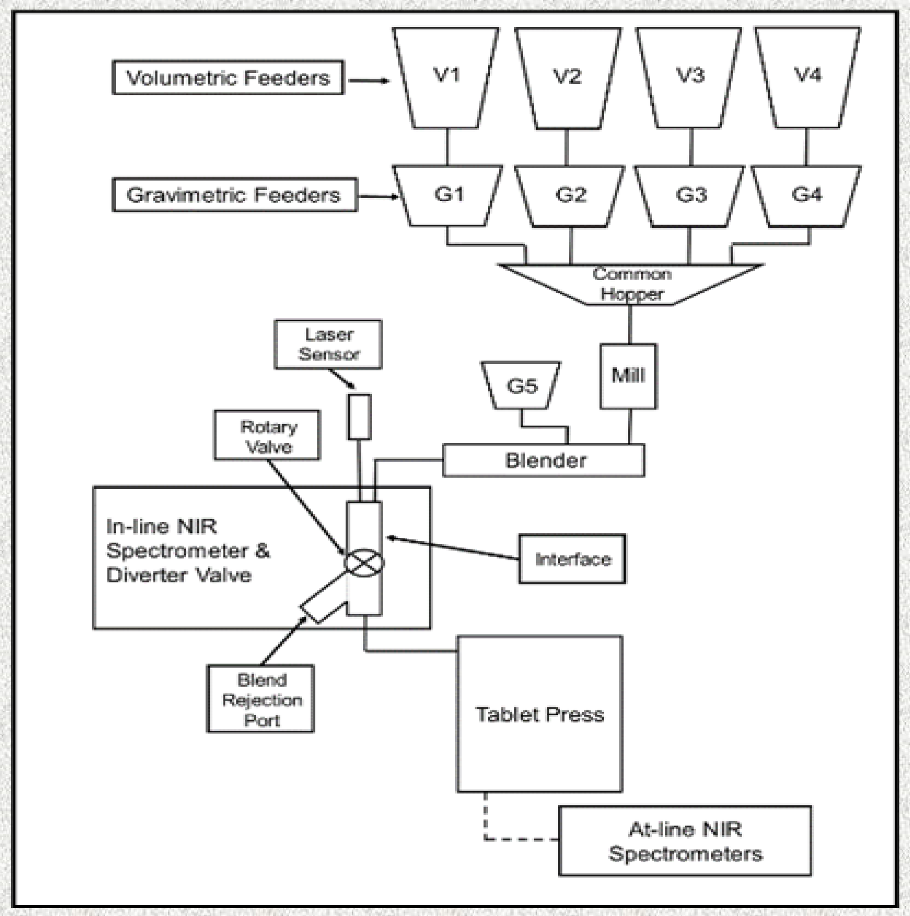
Table 2 List of Materials

Material Description	Composition (%W/W)	Feeder Dispenser #
Active Pharmaceutical Ingredient (API)	40-60	3
Filler	40-60	1
Disintegrant	2 – 5	5
Lubricant	1 – 2	2

The experiment consists of the following stages:

1. The desired process parameters were set according to the recipe at which the RTD will be determined for the system.
2. The PAT tool to monitor the concentration of the tracer at the system outlet was set and taking concentration measurements.
3. Start the CM process (Refer to figure 1) at the desired process parameters and wait until the process reaches a steady state (or control state).
4. Afterwards, change the concentration of the tracer at a time t=0 by changing the tracer's feed rate setpoint.
5. Collect samples for the time necessary for the change in tracer concentration to stabilize.
6. Determine the concentration of the samples collected during the experiment.
7. Create a concentration vs time plot to verify that the change in concentration can be observed in each of the experiments.

Figure 3 Diagram for the CM line



Results and Discussion

The first step to determine the RTD properties of an RTD function is pretreating the data. Distribution is a normalized function starting at the coordinate (0, 0) and ending at zero concentration. Furthermore, the area under the RTD function curve is equal to 1. For the step change, the data set is normalized by making the step change response start at zero (0) and end at one (1). This type of normalization is performed by rescaling the data with the following equation:

$$F(t) = \frac{C(t) - C_{beg}}{C_{end} - C_{beg}} \qquad (4)$$

After pretreating the RTD data, it was necessary to perform a model fitting of the RTD data using a RTD model (e.g., axial dispersion model). Data fitting was performed using a numerical computing software (i.e., MATLAB) that can solve nonlinear curve-fitting problems in least-squares sense.

Table 3 Fitted Models Parameters

Model	Axial Dispersion	
Equation	$E(\Theta) = \frac{1}{2\sqrt{\pi\Theta/Pe}} \exp\left\{-\frac{Pe(1-\Theta)^2}{4\Theta}\right\}$ where $\Theta = (t - t_{delay})/\tau$	
Parameters to be estimated	$t_{delay} =$	time that takes for the tracer to start entering the system of interest.
	$\tau =$	mean residence time of the system.
	$Pe =$	Péclet number

Blends spectra were analyzed to determine the Blend API concentration. A chemometric model was used to predict the Blends API concentration. A concentration vs time dataset was created and a RTD model was fitted to the data.

Figure 4 Experimental Results

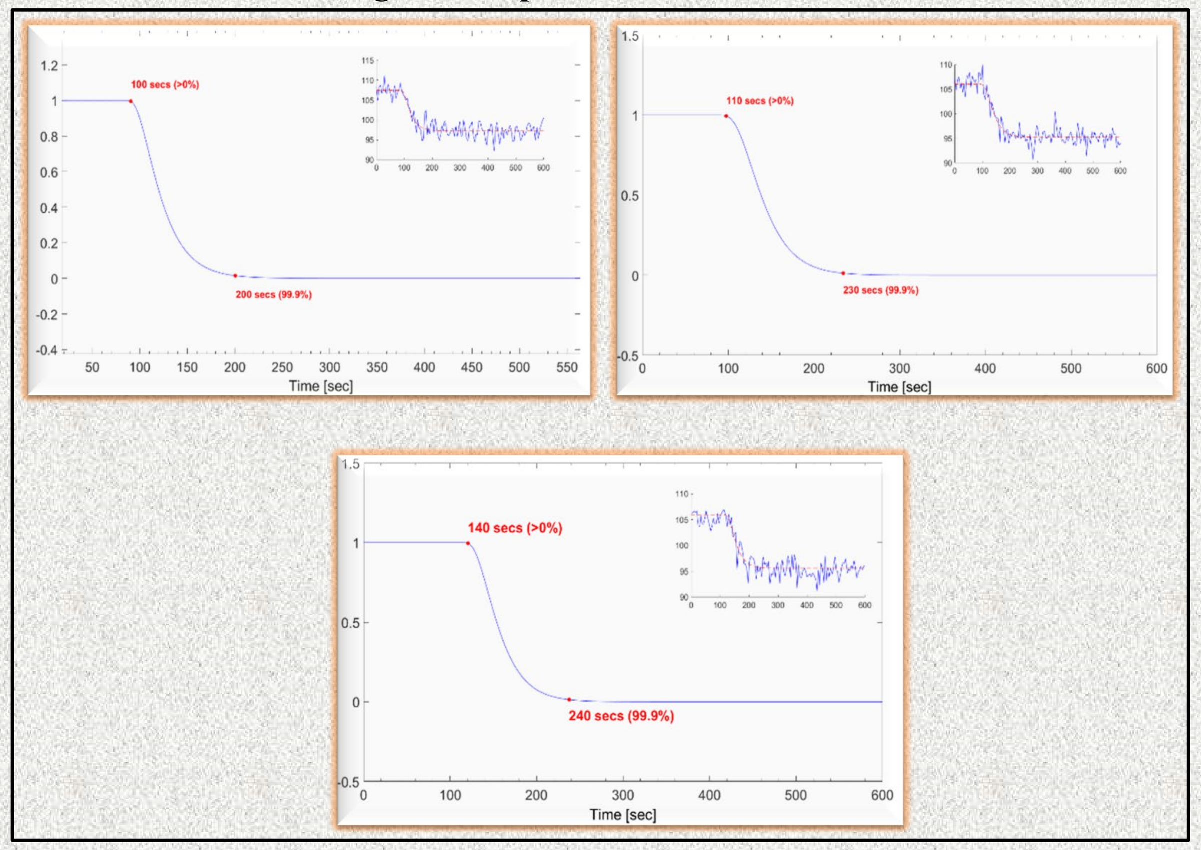


Table 4 Summary of Experiment Results

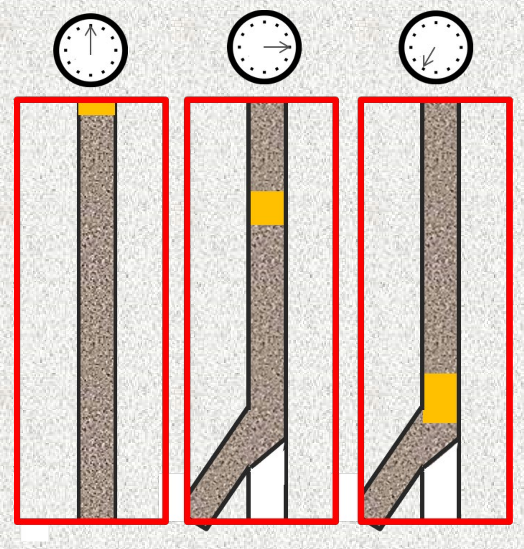
Experiment	ToR-0	ToR-99
Run 1	100	200
Run 2	110	230
Run 3	140	240

Factors in Experiment 1 (Run 1) provides the fastest Residence Time results. Factors in experiment 3 (Run 3) provides the slower Residence Time distribution studies. The target runs permit us to establish a center point to verify if the results obtained are within the expected range. The results show that at target condition the RTD is between Run 1 (Fast) and Run 2 (Slow). This information should be used in a control strategy to define when to reject and when to accept blended materials.

Conclusions

After applying RTD methodology, it was possible to develop a control strategy that permits to reject and accept material in a continuous manufacturing line. Based on gathered data the team was able to identify the areas that had the most impact in the RTD. Furthermore, the knowledge obtained during this study can be applied to a continuous manufacturing line to avoid excess of material waste. This helped to create possible solutions to new oral solids products. Residence Time Distribution studies were performed to understand the state of control interaction using mathematical modeling techniques and achieving a steady operation

Figure 5 Reject and Accept



Future Work

Even though the experiment was successful, there are opportunities available for future improvements. Additional information can be obtained from RTD studies that can support the design and operation of a continuous manufacturing line. For future projects the following information can be obtained:

- Reduce blending noise
- Reduce material waste
- Material Traceability

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