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

Elvin O. Almodovar Garcia
Manufacturing Engineering
Rafael Nieves, PharmD.
Industrial and Systems Engineering
Polytechnic University of Puerto Rico

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. Residence Time Distribution (RTD) looks at the dynamics of multiple integrated units and how material properties, equipment design and process parameters impact the flow of material through the 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.*

Key Terms *— Continuous Manufacturing, Control Strategy, Residence Time Distribution (RTD), Taylor Dispersion.*

PROJECT STATEMENT

Chemical and pharmaceutical processes form an essential part of the society. The need for new, effective, simpler, and modern processes makes these fields a fertile ground for different types of research and technologies. Pharmaceutical processes are characterized by the continuous development of technologies and innovative systems. In recent years, the implementation of techniques that permit the characterization and control of process has been used to continuously monitor the process **Error! Reference source not found.**. These new technologies required a change for a traditional industry were most of the pharmaceutical process are carried out in batch modes causing high cost and lower efficiency [1].

To achieve a continuous process, in the pharmaceutical manufacturing, several processes needs to be connected to achieve a constant product throughput. Some of these processes are granulation, feeding, mixing, compression, drying, and coating. A continuous mixing process required several unit operations to be connected, monitored, and controlled to maintain a certain throughput, concentration, and blend uniformity through the continuous line.

RESEARCH DESCRIPTION

In a continuous process any deviation from the intended process parameters can cause an unreliable product and economical losses **Error! Reference source not found.**. 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.

RESEARCH OBJECTIVES

The main objective of this research work is to utilize Residence Time Distribution to assess the control strategy of a direct compression line. Determining how to accept or discard blended material. The specifics objectives of this research work are the following:

- Develop and implement advanced controls based on the line Residence Time Distribution (RTD)

- Develop and implement controls to maintain the desired product Quality Attributes.
- Develop and implement a control strategy to maintain the homogeneity of the blend and allow the filtering of any material perturbation.

RESEARCH CONTRIBUTIONS

With this research different continuous manufacturing lines can be assessed to verify several attributes. The following attributes can be determined using the methodology explain in this research study:

- Understanding of our process mixing performance.
  - Mixing Behavior
  - Blender Filter Capability
- Feeding System understanding
  - Disturbances Filtering
  - Selection of Tolerance and Rejection Limits
- Control Strategy
  - When to reject or accept material
  - Process Design
  - Process Understanding

Another contribution of this research will be reducing waste and optimizing process since the RTD properties will provide sufficient information to understand when blended material should be rejected or accepted.

LITERATURE REVIEW

Continuous Manufacturing (CM) process technology is well-known and frequently used in the materials and food industry **Error! Reference source not found.Error! Reference source not found.**. The implementation of continuous manufacturing has the following potential benefits:

- Integrate several equipment's to reduce processing time and increase product quality
- Reduce operational space required by the traditional batch process.

In a continuous manufacturing process, the product:

- Flows between each of the inter-connected unit operations (Feeding, Blending, Compression)
- CQAs and Critical Process Parameters (CPPs) can be monitored online through the process

The RTD information can be used for material traceability, control strategy (e.g. control system decisions for accepting conforming material or rejecting non-conforming product), for evaluating mixing performance, and to determine the blender noise filtering capability for the feeders' mass flow variation **Error! Reference source not found.**.

Residence Time Distribution

Residence time distribution (RTD) is a distribution of how much time a material spends inside a unit operation. 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 **Error! Reference source not found.**. The RTD is defined as the probability distribution of time that a solid or fluid material stays inside a continuous flow system. To characterize the residence time distribution of a system, a "tracer" material is used to measure the time it takes for the material to travel through the continuous flow system.

Types of RTD Experiments

Two types of tracer experiments commonly employed to determine the RTD of a system are the pulse experiment and the step change experiment **Error! Reference source not found.Error! Reference source not found.**.

In a pulse experiment, an amount of tracer is quickly injected in the shortest time possible in one shot into the feed-stream of the system. The outlet concentration is then measured as a function of time. An example of a pulse injection and pulse response of a system is shown in Figure 1. Based on the pulse experiment, the output pulse response corresponds to the residence time distribution of the system.

Another way to determine the RTD of a system is through a step change experiment. In a step change experiment, a constant feed rate of the tracer is

injected into the feed-stream of the system at a time t=0. Just like in the pulse experiment, the outlet concentration is then measured as a function of time. An example of a step change injection and step change response of a system is shown in Figure 2. Compared to the pulse response, which is the RTD of the system, the step change is in fact the probability cumulative distribution of the system.

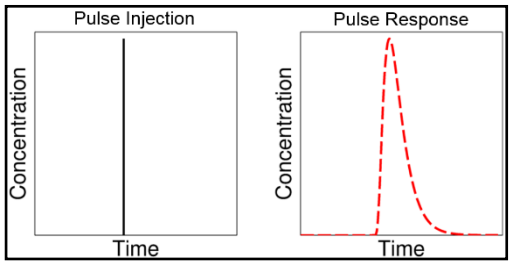

Figure 1
Pulse Experiment

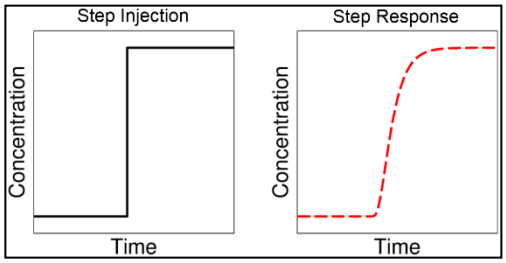

Figure 2
Step Change Experiment

Residence Time Distribution Function Error! Reference source not found.

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

$$E(t) = \frac{C(t)}{\int_0^\infty C(t)dt} \quad (1)$$

where C(t) is the tracer's concentration as a function of time. The RTD function is defined by normalizing the concentration function of the tracer. Therefore,

$$\int_0^\infty E(t)dt = 1 \quad (2)$$

This aspect of the RTD function indicates that eventually the tracer amount injected to the system must leave the system. The RTD function *E(T)* is determined from a pulse experiment. Otherwise, the step change experiment determines the cumulative RTD function, identified as *F(T)* There is an integral relationship between the RTD function, and the cumulative RTD function given by:

$$\int_0^t E(t)dt = F(t) \quad (3)$$

Just as the RTD function is the normalized response of the pulse injection, the cumulative RTD function is the normalized response of the step change injection.

Characteristics of the RTD

Two common parameters used to characterize and compare different RTDs are the mean residence time (τ) and the mean centered variance (σ^2) (square of standard deviation). The equations for the mean residence time (τ or MRT) and mean centered variance (σ^2 or MCV) are as follows:

$$\tau = \int_0^\infty tE(t)dt \quad (4)$$

$$\sigma^2 = \int_0^\infty (t-\tau)^2 E(t)dt \quad (5)$$

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. Another way to evaluate the spread of the distribution is through the standard deviation (SD) which is the square root of the mean centered variance **Error! Reference source not found. Error! Reference source not found. Error! Reference source not found.**[7].

Residence Time Distributions can also be characterized through the Residence Time of 0% and 99% of the tracer distribution of the system (ToR0 and ToR99). The ToR0 is the time it takes the tracer material to start exiting the corresponding system under evaluation. The ToR99 is the time it takes for 99% of the tracer material to go through the corresponding system under evaluation. These two mathematical relations are critical to create a robust

control strategy since it will ensure that any blend variability will not be further process.

Modeling of the RTD Function

There are different models used to describe the non-ideal behavior of the tracer material in a system. For continuous manufacturing processes, the two most employed models are the CSTR-in-series model (CSTR stands for Continuously Stirred Tank Reactors) and the axial dispersion model (also known as the Taylor dispersion model). In this study to describe the non-ideal behavior of the tracer material in a system we used the axial dispersion model, also known as the Taylor dispersion model, which is described by the following equation:

$$E(\Theta) = \frac{1}{2\sqrt{\pi\Theta/Pe}} \exp\left\{-\frac{Pe(1-\Theta)^2}{4\Theta}\right\} \qquad (6)$$

Where *Pe* represents the Péclet number. *Pe* is a dimensionless parameter that represents the ratio of the rate of convection of the material by the feed-stream in the system to the rate of diffusion of the same material driven by an appropriate gradient**Error! Reference source not found.** [7].

The CSTR-in-series and the Taylor dispersion models can be applied for fitting the experimental RTD data of various systems. However, deciding on which model to use will depend on the fitting accuracy

METHODOLOGY

The RTD of a continuous flow system can be determined by performing a step change experiment. A screening design at the extreme levels of (Throughput and Blender Speed) was executed to determine the space where we can expect our Residence Time distribution. This experiment will consist of three (3) runs: one (1) run at low Line Throughput (-1) and low Blender Speed (-1), one (1) run at target Line Throughput (0) and target Blender Speed (0), and one (1) run at high Line Throughput (1) and high Blender Speed (1) to evaluate the Residence Time distribution. In each of these runs a concentration step change will be forced to determine the RTD of the line. All factors are coded variables. Refer to Table 1 for a summary of the experiment design.

Table 1
Experiment Design Factors

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

Continuous Manufacturing System

The continuous system included four gravimetric feeders, as shown **Error! Reference source not found.**. The CM process consisted of pneumatic transfer of the API and excipients from their container to volumetric feeders coupled to gravimetric feeders. The gravimetric feeders added the API, filler, disintegrant, and lubricant to create the desired drug product formulation. The gravimetric feeder operated under two modes: gravimetric (feeding material to the line) and volumetric (refill cycle). The loss in weight (LIW) control was used when the feeder was in the gravimetric mode. This LIW control involved the use of the weight measured by the weight bridge. LIW determined the rate at which the material decreased in the feeder to update the screw speed and maintain the mass flow rate. After the gravimetric feeders, the API and excipients passed to an in-line manually controlled conical mill and then entered an in-line continuous paddle blender. The NIR spectrometer was installed after the blender. The blend level in the interface was maintained by controlling the rpm of the rotary valve with a laser level sensor. The blend moved by the rotary valve passed through the diverter valve for waste (blend rejection port) or towards the tablet press for production **Error! Reference source not found.**.

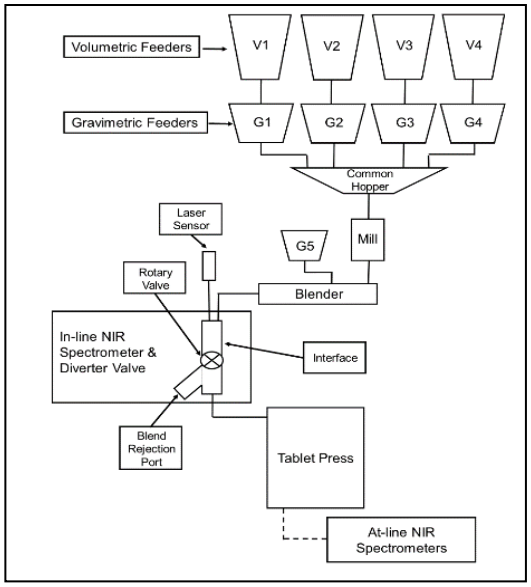

Figure 3

Diagram for the CM line Error! Reference source not found.

Formulation

This study will be conducted using the following formulation. Step change experiments will be performed modifying the composition of the API in 10 percent increase and decrease. When a modification in the API is required the filler composition will be changed to maintain the required total line throughput at the same level. Refer to Table 2 below for a list of materials.

Table 2

Material Formulation Description

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

Line Recipes

Six (6) different line recipes were created to execute the RTD study. The recipes consist of the feeder setpoints and corresponding percent as per experiment. Refer to Table 3 below for a summary of the recipes created.

Table 3

Recipes

Recipe Name	Line Throughput (Kg/h)	API %w/w	Blender Speed
LowThrou-LowAPI	-1 (Low)	95	-1 (Low)
LowThrou-HighAPI	-1 (Low)	105	-1 (Low)
TargetThrou-LowAPI	0 (Target)	95	0 (Target)
TargetThrou-HighAPI	0 (Target)	105	0 (Target)
HighThrou-LowAPI	1 (High)	95	1 (High)
HighThrou-HighAPI	1 (High)	105	1 (High)

Experiment Execution

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. For the step change experiment, one of the parameters is the tracer's feed rate: In step change experiments, the throughput is commonly desired to remain constant. If this is the case, the feed rate of one or more raw materials (apart from the tracer) of the product formulation must be adjusted to compensate for the change in the tracer's feed rate.
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 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.

RESULTS AND DISCUSSION

This section presents the findings of this research work by using the RTD methodology.

Data Analysis and Data Pretreatment

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. Therefore, pretreatments must be performed to the RTD data in order to have the normalized form of the data. The pretreatments to be performed are the following:

Step Change Experiment

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:

$$F(t) = \frac{C(t) - C_{beg}}{C_{end} - C_{beg}} \qquad (10)$$

where C(t) is the concentration of the tracer as a function of time, C_{beg} is the concentration at the start of the step change and C_{end} is the concentration and the end of the step change.

Model Fitting

After pretreating the RTD data, it will be necessary to perform a model fitting of the RTD data using a RTD model (e.g., axial dispersion model). The drivers to perform model fitting are based on the fact that if the RTD properties (e.g., MRT, MCV, SD, ToR0 and ToR99) are calculated with the pretreated data, there may be errors in the estimation of the RTD properties due to the noisy nature of the concentration measurements.

Data fitting was performed using a numerical computing software (i.e., MATLAB) that can solve nonlinear curve-fitting problems in least-squares sense. For this least-squares curve fitting problems, the model function to fit the data was defined. Based on the RTD models discussed, the model functions used and the parameters that fit the RTD data is shown in

Table **4**.

Table 4

Model Functions and Parameters for Least-Squares Curve Fitting

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

Figure 4 shows examples of the model fitting to step change and pulse experiments data. After obtaining the model fit, the MRT, MCV, ToR_0 and ToR_{99} can then be calculated for the fitted data.

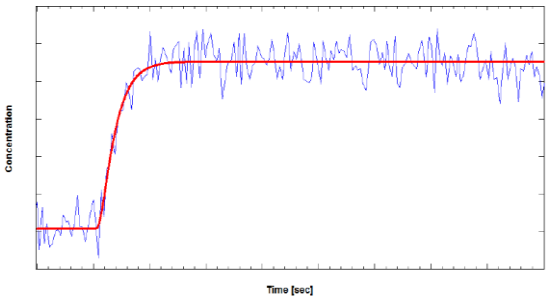

Figure 4
RTD Fit Results for Both Step Change and Pulse Responses

Actual Results

As mentioned in Section 3, the goal of this study was to determinate the RTD to create control strategy. The time delay was evaluated by a step change at three different conditions. The time that the step change takes from the sensing interface to the diverter valve was measure with the PAT analyzer.

The CM line startup condition was made using a recipe corresponding to 105% API Concentration. At startup, the line was operated until the feeders stabilized. Immediately after, a step change experiment was initiated, and the blend sample collection started. Different throughputs (high – run 1, target – run 2 and low – run 3) were tested at different blender speeds (high – run 1, target – run 2 and low – run 3).

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 5, Figure 6, and Figure 7 show the zero time (ToR-0) and ToR-99 results obtained from the analysis of the RTD.

With the information obtained from the RTD properties the time delay measurement can be estimated. The zero time (ToR-0) and ToR-99 can also be estimated. The time delay is the estimated time to react if a disturbance is seen at the sensing interface.

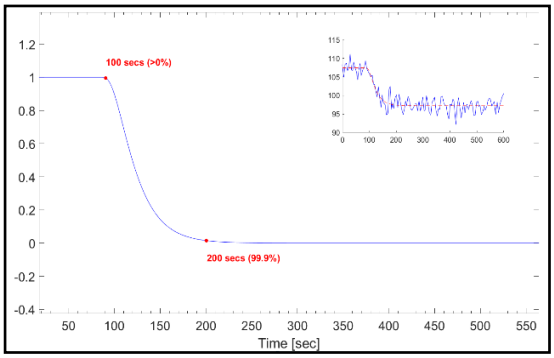

Figure 5
RTD fit of CM line Concentration Step Change (Run 1)

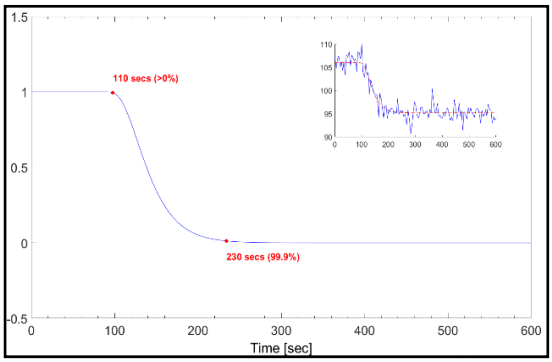

Figure 6
RTD fit of CM line Concentration Step Change (Run 2)

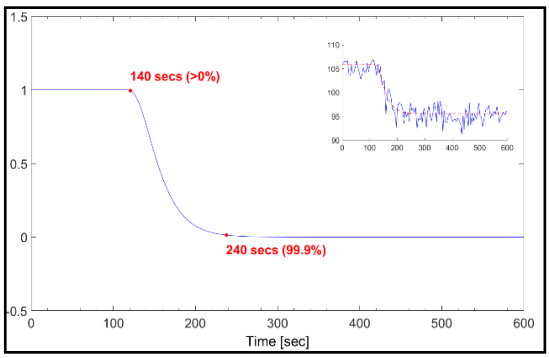

Figure 7
RTD fit of CM line Concentration Step Change (Run 3)

Table 5
Experiment Results

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

Table 5 shows the experiment results. Factors in Experiment 1 (Run 1) provides the fastest Residence Time results. This information shows us that at least the control system had 100 seconds to react to any perturbation. For example, if a feeding perturbation is detected at the feeder's stage material should be rejected after 100 seconds. Factors in experiment 3 (Run 3) provides the slower Residence Time distribution studies. After a perturbation is observed in the CM line at least we need to wait 240 seconds to remove this perturbation from the line. For example, after a perturbation is detected at least 240 seconds should be wait until all blended materials conforms with the expected attributes. 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.

CONCLUSION

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.

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

REFERENCES

[1] Y. Gao, A. Vanarase, F. Muzzio, and M. Ierapetritou, "Characterizing continuous powder mixing using residence time distribution," *Chem. Eng. Sci.*, vol. 66, pp. 417–425, Feb. 2011.

[2] F. J. Muzzio and M. G. Ierapetritou, "Scale-up strategy for continuous powder blending process," *Powder Technol.*, vol. 235, pp. 55–69, Feb. 2013.

[3] K. Järvinen, W. Hoehe, M. Järvinen, S. Poutiainen, M. Juuti, and S. Borchert, "In-line monitoring of the drug content of powder mixtures and tablets by near-infrared spectroscopy during the continuous direct compression tableting process.," *Eur. J. Pharm. Sci.*, vol. 48, pp. 680–8, Mar. 2013.

[4] H. Fogler, "Distributions of Residence Times for Chemical Reactos," in *Elements of Chemical Reaction Engineering*, 4th ed. New Jersey, Prentice Hall, 2006, ch. 13, pp. 867–944.

[5] Y. Gao, F. J. Muzzio, and M. G. Ierapetritou, "A review of the Residence Time Distribution (RTD) applications in solid unit operations," *Powder Technol.*, vol. 228, pp. 416–423, Sep. 2012.

[6] W. Engisch and F. Muzzio, "Using Residence Time Distributions (RTDs) to Address the Traceability of Raw Materials in Continuous Pharmaceutical Manufacturing.," *J. Pharm. Innov.*, vol. 11, pp. 64–81, Mar. 2016.

[7] E. W. Weisstein. Convolution Theorem [Webpage]. Available: http://mathworld.wolfram.com/ConvolutionTheorem.html

[8] J. M. Vargas *et al.*, "Process analytical technology in continuous manufacturing of a commercial pharmaceutical product," *Int. J. Pharm.*, vol. 538, pp. 167–178, Mar. 2018.