



Short communication

A dimensionless analysis of residence time distributions for continuous powder mixing



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ARTICLE INFO

Article history:

Received 19 January 2017

Received in revised form 18 March 2017

Accepted 1 April 2017

Available online 6 April 2017

Keywords:

Continuous pharmaceutical manufacturing

Residence time distribution (RTD)

Axial mixing

ABSTRACT

For continuous manufacturing of pharmaceuticals, understanding the dynamics of how a material flows through the process is critical with respect to the development of a control strategy for product quality assurance. Such understanding of the process dynamics can be obtained by characterization of the residence time distribution (RTD). The RTD for a process is not fixed and can vary due to changes in operating conditions or physiochemical properties of the blend. As such the RTD needs to be evaluated over the range of operating condition that can impact process dynamics (e.g. throughput, impeller rotation rate etc.). In this paper, we demonstrate that the dimensionless RTD (normalized with respect to the mean residence time) is invariant with throughput and impeller rotation rates under certain conditions for the two continuous direct compression processes. We present a case study to illustrate the utility of this relationship for predicting the process dynamics at different operating conditions (i.e., throughputs) and evaluating the impact of variations in the process dynamics on the control strategy for a continuous direct compression process.

Published by Elsevier B.V.

1. Introduction

Continuous manufacturing has been recognized as an emerging pharmaceutical technology that has a great deal of potential to improve agility, flexibility, and robustness in the manufacture of pharmaceuticals, offering benefits to both industry and patients [1,2]. Over the past decade, collaborative efforts by industry, academia, and regulatory agencies have made continuous manufacturing a reality in the pharmaceutical industry [3]. In continuous manufacturing processes a series of unit operations are connected to form an integrated manufacturing system, raw materials are continuously charged into the system, and products are continuously discharged from the system throughout the duration of the process [2].

For continuous manufacturing processes, understanding process dynamics in relation to material properties, equipment design, and process conditions is fundamental to understanding potential risks of continuous manufacturing to product quality, largely because of their potential impact on material traceability and disturbance propagation. Such understanding can be obtained by characterization of the residence time distribution (RTD). The RTD [4] is a probability distribution

function that describes the amount of time a solid could spend inside of a unit operation. The RTD can be used to characterize axial mixing to predict how fluctuations in a feeder dissipate in a mixer and their subsequent impact on the blend and content uniformity. It can also be used to track materials through the process and potentially isolate materials when specifications are not met. Therefore, the ability to adequately isolate and reject out-of-specification materials depends significantly on the knowledge of the RTD, and constitutes one key aspect of a control strategy for continuous manufacturing processes.

The RTD depends on the equipment design, operating conditions, and the physiochemical properties of materials [5]. For a given continuous manufacturing process and formulation design, the RTD can vary due to changes in the operating condition, such as decreasing or increasing the throughput to achieve the required production rate. Therefore, it is important to evaluate the RTD over the range of planned operating conditions, in addition to the RTD at the nominal operating condition. A continuous direct compression process has been one of the most common approaches to date for the commercial implementation of continuous manufacturing for immediate-release solid oral products. This process begins with the feeding of individual raw materials (i.e. solid API and excipients) into the system using loss-in-weight feeders. The materials are then mixed in a continuous mixer to achieve a uniform distribution of the API and excipients. A blend exiting the mixer is transferred directly to a tablet press to be compacted into tablets.

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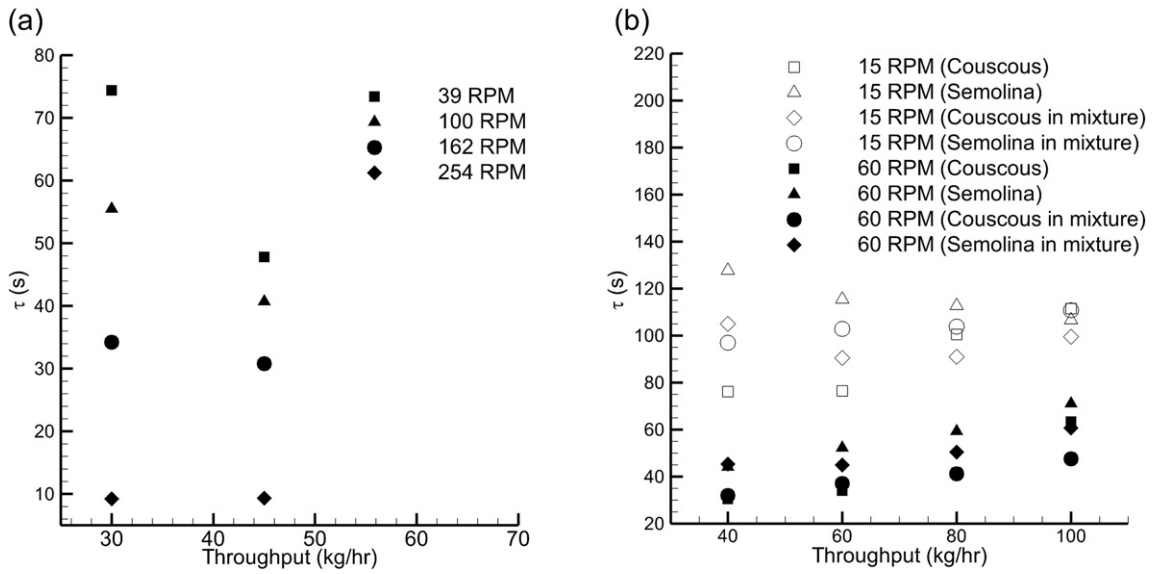


Fig. 1. Effect of throughput on mean residence time (a) Varnarase and Muzzio [5] and (b) Marikh et al. [6].

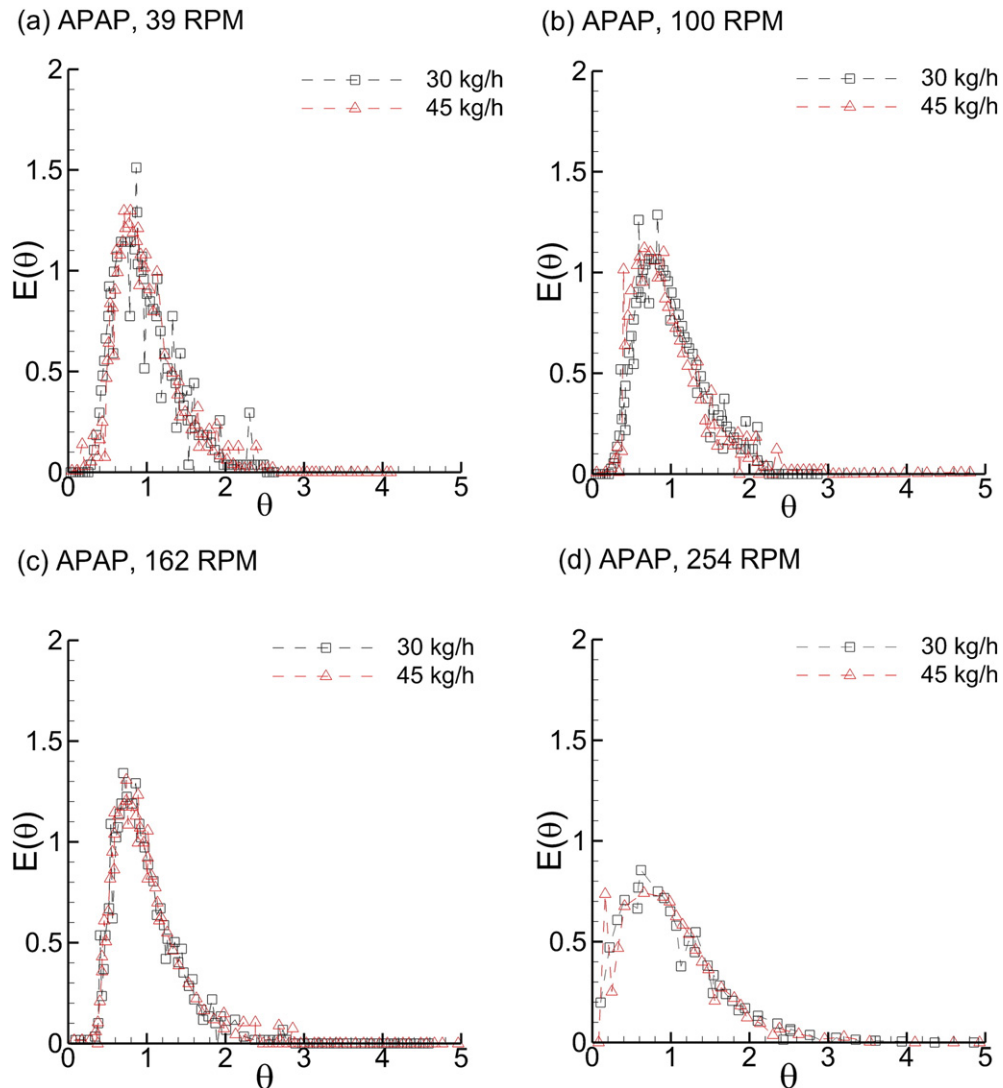


Fig. 2. Non-dimensionalization of the RTD from Varnarase and Muzzio [5].

In this study, we focus on characterizing the RTD at different operating conditions for continuous direct compression processes. The experimentally measured RTDs for two continuous direct compression processes reported in the literature (Vanarase and Muzzio [5] and Marikh et al. [6]) were non-dimensionalized by scaling to each distribution with its respective mean residence time, in order to better compare the flow behavior and mixing performance at different operating conditions. The dimensionless RTDs were found to be highly similar across different throughputs for a given impeller rotation rate. The results suggest that the dimensionless RTD can potentially be used to predict the process dynamics at different throughputs, once the RTD is measured at the nominal operating condition. A case study is presented to illustrate the use of the dimensionless RTD in predicting the process dynamics at different operating conditions (i.e., throughputs) and evaluating the impact of variations in the dynamics on the control strategy for a continuous direct compression process.

2. Methods

2.1. Non-dimensionalization of RTD

The purpose of creating a dimensionless RTD is that the mixing performance can be better compared at different operating conditions

because the mean residence time is eliminated as a variable. A dimensionless RTD, $E(\theta)$, can be defined as

$$E(\theta) = \tau E(t), \quad (1)$$

where $E(t)$ is a dimensional RTD curve and τ is mean residence time. The dimensionless time θ is given by

$$\theta = \frac{t}{\tau}, \quad (2)$$

The mean residence time (τ) is calculated using the definition on the first moment of the RTD ($E(t)$).

$$\tau = \int_0^{\infty} tE(t)dt, \quad (3)$$

2.2. Material traceability

The traceability of incoming materials in a continuous manufacturing process can be related to the overall residence time distribution. Tracing raw material composition allows for product lot-to-lot delineation based on time and lots of raw material used [7]. If the system response is linear, two successive tracer experiments with two different

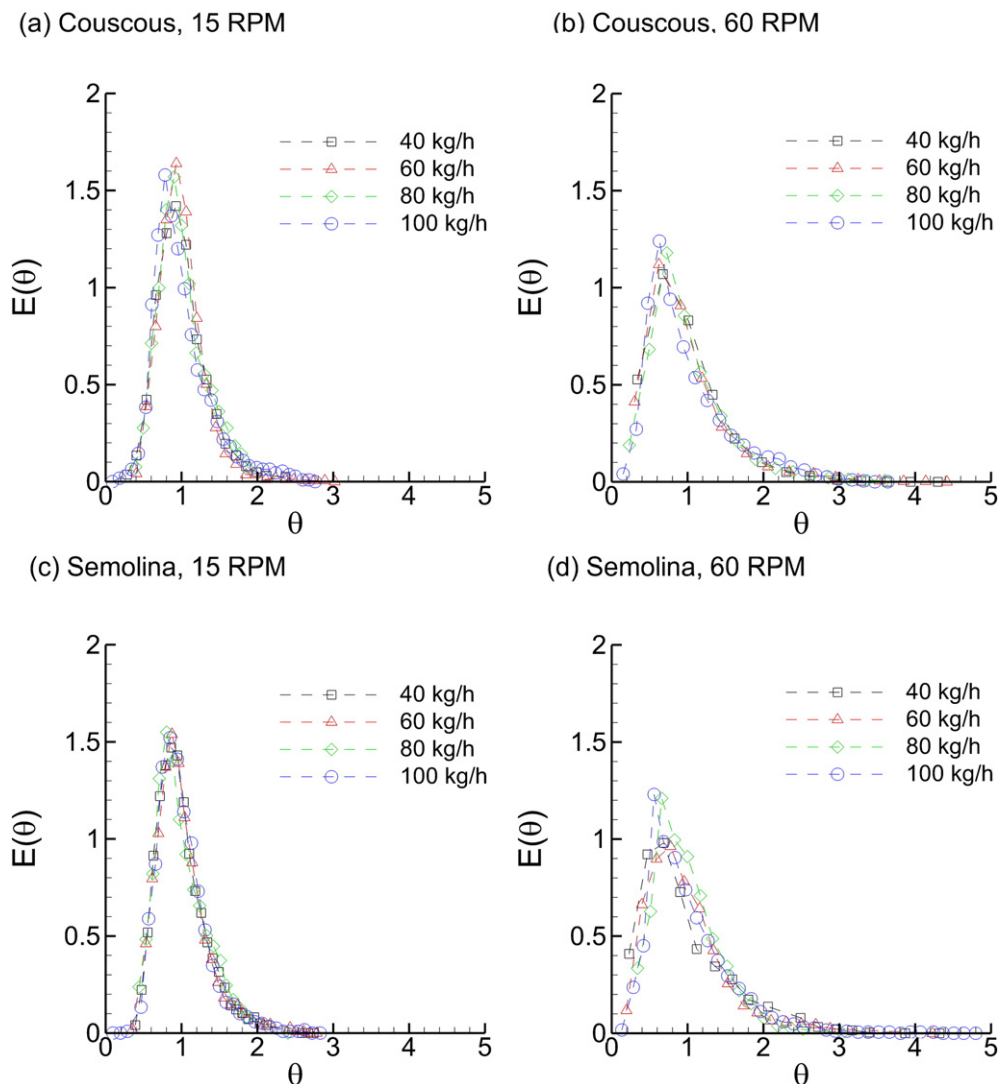


Fig. 3. Non-dimensionalization of the RTD measurements for couscous and semolina from Marikh et al. [6].

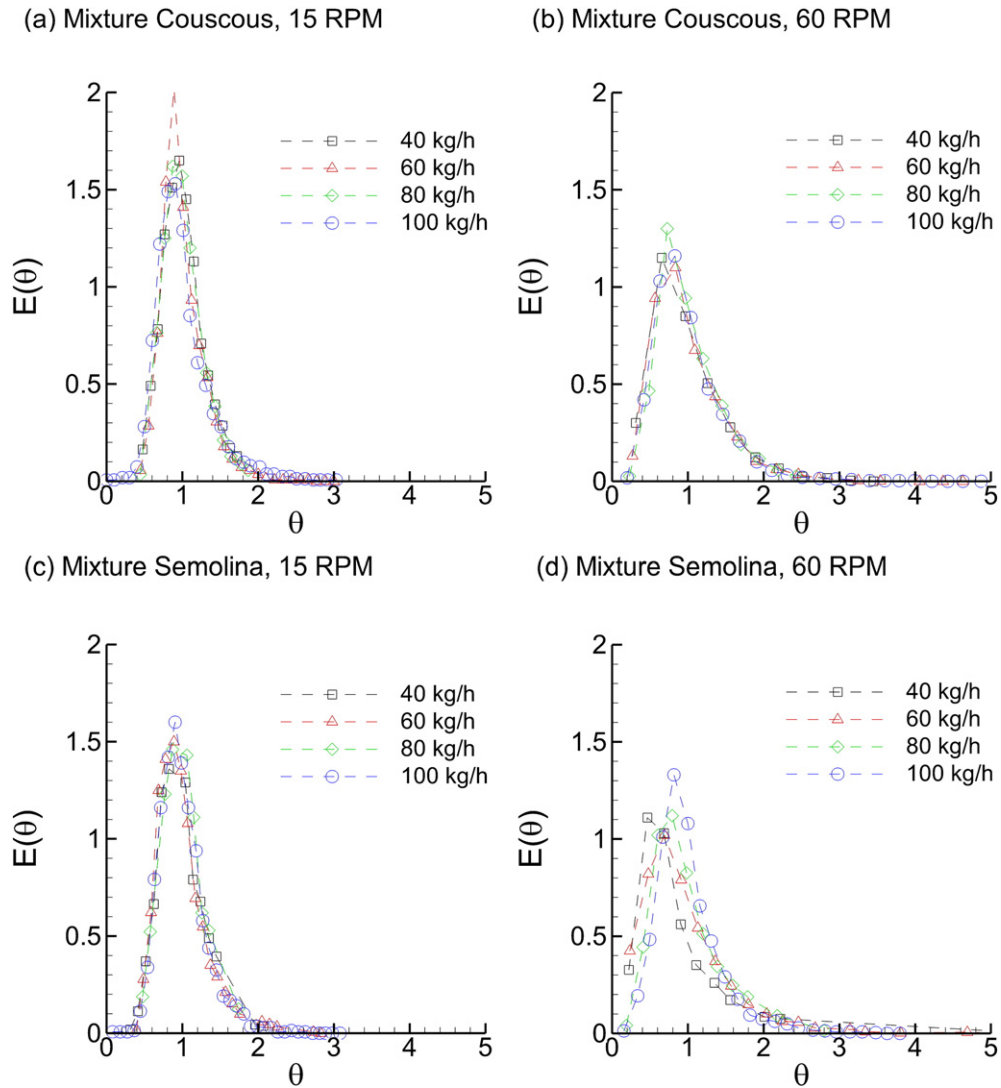


Fig. 4. Non-dimensionalization of the RTD measurements for couscous and semolina in a 50/50 mixture of couscous and semolina from Marikh et al. [6].

magnitudes of pulses or step changes should give the same $E(t)$ curve. The concentration profile at the outlet of a unit operation $C_{out}(t)$ can then be predicted by convolution of the concentration profile at the inlet of the unit operation $C_{in}(t)$ and the RTD:

$$C_{out}(t) = C_{in}(t) * E(t) = \int_0^t C_{in}(t-\tilde{t}) E(\tilde{t}) d\tilde{t} \tag{4}$$

This can be extended to the process with a series of unit operations to obtain an overall RTD by convolution of individual unit RTDs recursively:

$$E(t) = E_1(t) * E_2(t), \tag{5}$$

where $E_1(t)$ and $E_2(t)$ represent RTDs from sequential unit operations.

3. Results

3.1. Analysis of RTDs in dimensionless form

In the first part of this investigation, we systematically examined the dynamics of material flow with respect to the mean residence time for

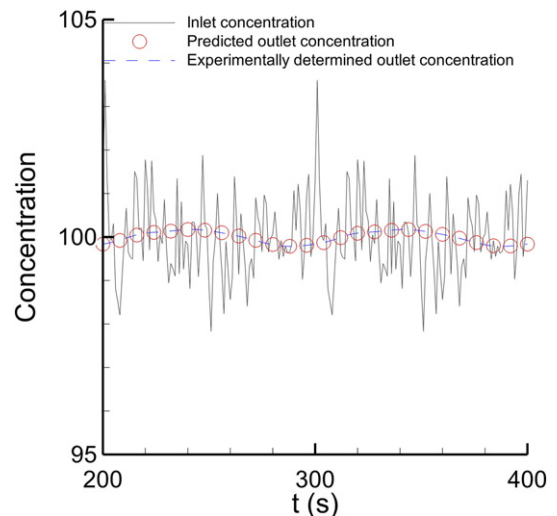


Fig. 5. Predicted and experimentally determined values of output concentration after reaching the target operating condition for APAP, given an inlet concentration.

Table 1
Powder materials used in [5,6].

Material	Mean particle size (um)	Bulk density (g/mL)
Acetaminophen (APAP)	45	0.39
Couscous	1400	0.72
Semolina	340	0.76

different operating conditions. There are a few sets of experimental RTD data reported in literature, characterizing the process dynamics for continuous pharmaceutical manufacturing processes. Recent experimental studies investigated the influence of operating and design parameters of continuous mixing on the RTD [5,6]. Vanarase and Muzzio [5] conducted RTD experiments for acetaminophen (APAP) in a Gericke GCM 250 continuous mixer for eight different conditions (four different impeller rotation rates: 39, 100, 162, and 254 RPM at two throughput levels: 30 and 45 kg/h). Similarly, Marikh et al. [6] measured eight experimental RTDs for semolina and couscous as well as for 50/50 mixtures of these materials in a Gericke GCM 500 continuous mixer (four different throughputs: 40, 60, 80, 100 kg/h at two different impeller rotation rates: 15 and 60 RPM).

Each RTD reported in Vanarase and Muzzio [5] and Marikh et al. [6] is non-dimensionalized based on its respective mean residence time. The mean residence time is calculated from the first moment of the experimental RTD data corresponding to each set of operating conditions using Eq. (3). The calculated mean residence times are shown in Fig. 1a and b for each set of operating conditions. Fig. 1 shows relationships between mean residence time and throughput. As shown in Fig. 1a (APAP), mean residence time increases with decrease in throughput at the lower impeller rotation rates (39, 100, and 162 RPM), and mean residence time does not change between the two throughputs at the highest impeller rotation rate (254 RPM). It is seen from Fig. 1b (semolina and couscous) that the mean residence time increases linearly with increases in throughput at the impeller rotation rate of 60 RPM. However, a non-linear behavior of mean residence time as a function of throughput is observed at the very low impeller rotation rate of 15 RPM. Regardless of the correlation between mean residence time and throughput, our analysis shows that RTDs in a dimensionless form are highly similar at different throughputs for each impeller rotation rate, as shown in Figs. 2–4. A similarity factor (f_2) [8] was used to compare the dimensionless RTDs at each impeller rotation rate. The similarity factor f_2 value was found to be >50 at each impeller rotation rate which denotes that the curves are similar.

We also conducted the following analysis as an alternative way to assess the similarity of the dimensionless RTDs measured at different throughputs. As an example for illustration, the RTD at a throughput of 45 kg/h and a impeller rotation rate of 100 RPM from the Vanarase

and Muzzio [5] study was predicted by rescaling the dimensionless RTD measured at a throughput of 30 kg/h and a impeller rotation rate of 100 RPM with the mean residence time for the 45 kg/h throughput case. This predicted RTD was then compared to the experimentally measured RTD at 45 kg/h to determine if the two RTDs yielded similar predictions for the dampening of input feeder fluctuation during the continuous blending process step as shown in Fig. 5. The predicted and experimentally measured RTD yielded similar results for the expected output concentration profile with a root mean squared difference of 0.002. We also carried out this analysis for the group of dimensionless RTDs with lowest similarity score represented by the conditions in Fig. 4d. In this case, the predicted and experimentally measured RTD again yielded similar results for the expected output concentration profile but with a larger root mean squared difference of 0.006.

The powder materials used in the RTD experiments of Vanarase and Muzzio [5] and Marikh et al. [6] are listed in Table 1. These powders were chosen to test a range of cohesiveness and flowability in the experiments. With respect to the flowability index, the couscous is a free flowing product, while semolina and acetaminophen exhibit a cohesive behavior. Moreover, these two studies were performed on two different sizes of mixers, Gericke GCM 250 and GCM 500, respectively. The GCM 250 is 0.33 m long and 0.1 m diameter whereas the GCM 500 is 0.5 m long and 0.2 m diameter. The observation that the dimensionless RTD curves overlap each other at different throughputs for each impeller rotation rate appears to hold for different sizes of mixers and a seemingly wide range of granular matter, from fairly small acetaminophen to relatively large and dense particulates such as couscous. This is consistent with the finding of Abouzeid et al. [9], suggesting that the residence time distribution is independent of particle size for rotary drum devices.

These observations suggest an interesting relationship, showing that the dimensionless RTD is independent of throughput when the impeller rotation rate is kept the same. Provided that the correlation of the mean residence time as a function of throughput is established (e.g., by design of experiments (DOE) where the mean residence time may be simply calculated from hold-up measurement (hold-up (kg)/throughput (kg/h)) rather than tracer RTD experiments to obtain the distribution), this relationship can be used for predicting the process dynamics at different throughputs for a given impeller rotation rate, once the RTD is measured at the nominal throughput. The case study below illustrates the potential utility of this relationship in the development of a continuous manufacturing process.

3.2. Continuous direct compression: a case study

The experimental RTDs for the continuous manufacturing process at the target throughput were determined by introducing a step change in

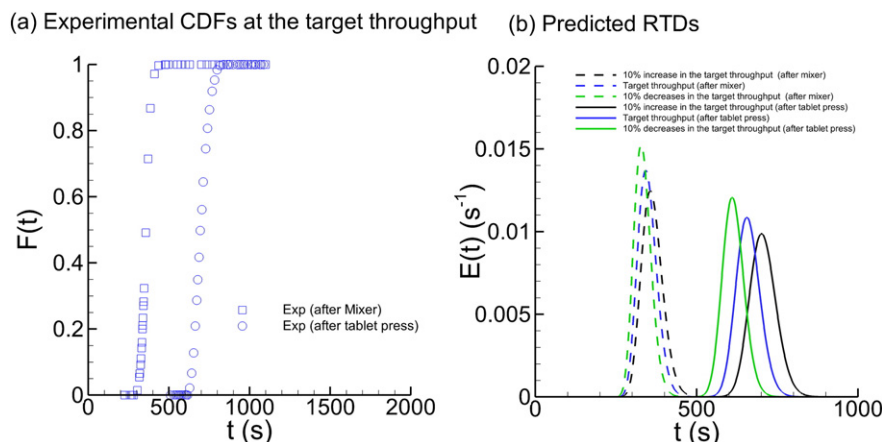


Fig. 6. (a) Experimental cumulative distribution function (CDF) for the RTD at the target throughput after mixer and tablet press, (b) Predicted RTDs after mixer and tablet press for $\pm 10\%$ changes in the target throughput. As a note, the RTD data has been shifted to the right by a pre-set amount to blind the source of the data.

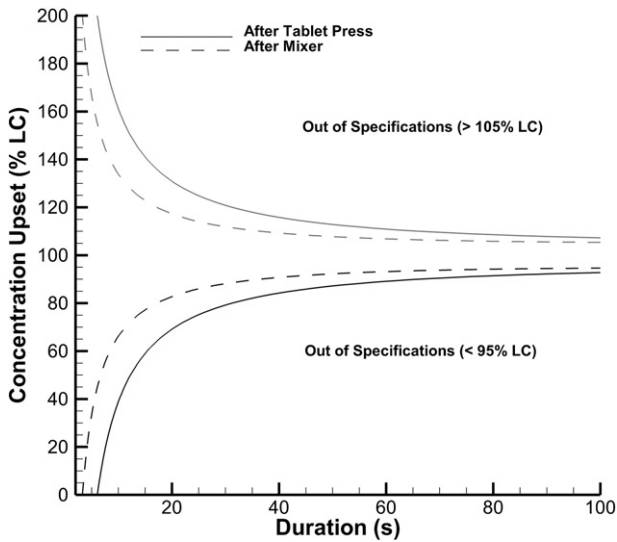


Fig. 7. Impact of a disturbance of a certain duration on the concentration after mixer and tablet press at the target throughput.

the concentration of an API and measuring the response after the mixer and the tablet press, respectively (Fig. 6a). To show that the process dynamics at difference operating points can be predicted, once the RTD is measured at the target throughput, the impact of a $\pm 10\%$ in the target throughput was examined. The RTDs after the mixer and the tablet press at the target throughput were transformed into the dimensionless RTDs. After which the RTDs at $\pm 10\%$ of the target throughput were then predicted at the exit of the mixer and the tablet press by scaling the dimensional RTDs at the target throughput with a mean residence time that was adjusted by $\pm 10\%$ compared to the mean residence time at the target throughput (Fig. 6b). This case assumed a linear correlation between the mean residence time and throughput, which was confirmed subsequently by a DOE study (data not shown) where throughput was one of the parameters varied. Over short ranges of throughput as examined in this case study, a linear relationship is likely to hold between mean residence time and throughput (see Fig. 1). As noted in the previous section, regardless of the type of relationship between mean residence time and throughput (e.g. linear or non-linear), as long as the relationship is known, the analysis shows that RTDs in a dimensionless form can be used to predict the RTD for the process at a new throughput.

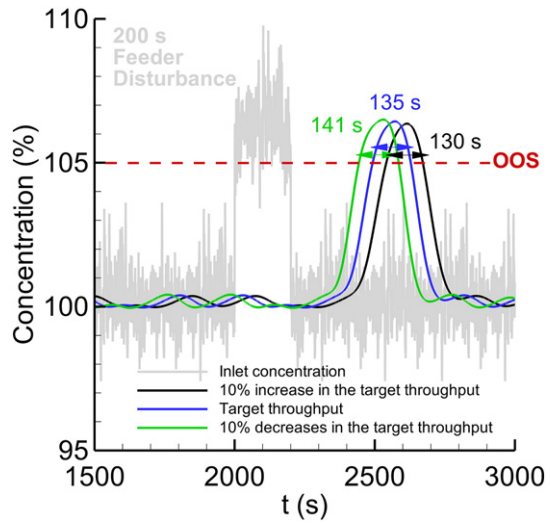


Fig. 9. The times for which the product is out-of-spec at the target throughput and $\pm 10\%$ changes in the target throughput after tablet press.

Once RTD is established, the output concentration can be predicted by convolving the input concentration and the RTD. Given the dynamic nature continuous manufacturing processes, it is expected that the amplitude and duration of the disturbances in concentration need to be considered. The RTD model can be used to evaluate the impact of a disturbance in the feeder on the concentration at the exit of either the mixer or the tablet press. Fig. 7 illustrates that the determination of out-of-specification (OOS) products depends largely on the amplitude and duration of the disturbance. A short-duration low-amplitude fluctuation from the feeders will not lead to product results falling outside of the pre-specified limits (e.g. 95% to 105% for assay) at the tablet press due to mixing occurring throughout the continuous system. For example, a disturbance with a magnitude of 120% assay label claim (% LC) and duration of 15 s will not cause the tablets to be OOS after the tablet press. Using this approach, material that is outside of a pre-specified blend uniformity acceptance criteria should be diverted. From this figure, it was also observed that the area inside of the pre-specified limits increases from the mixer to the tablet press. This indicates that the mixing in the feed frame of the tablet press is able to further dampen the feeding fluctuations.

Changes in process operating conditions can impact the process dynamics and thus the impact of feeding disturbances on product quality.

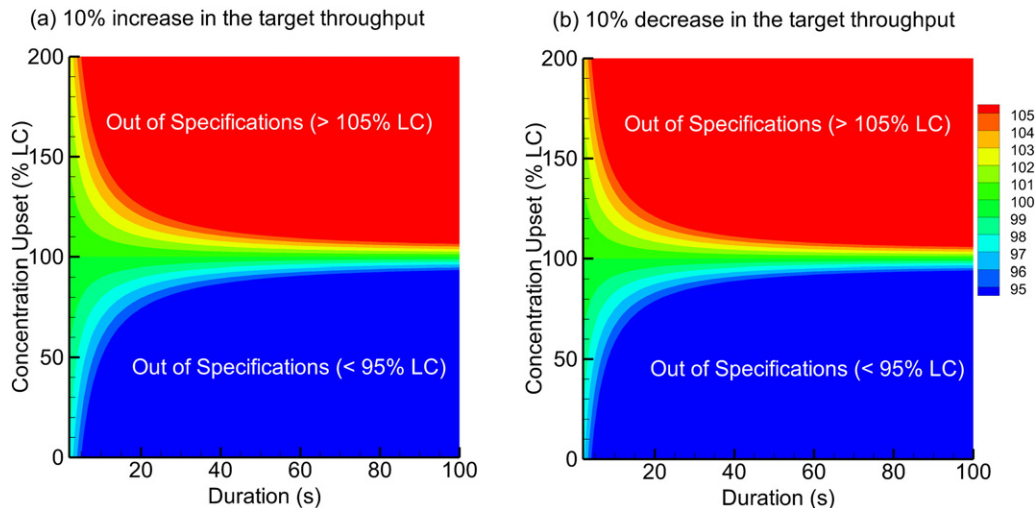


Fig. 8. Impact of a disturbance of certain duration on the concentration after the tablet press, with (a) 10% increase in the target throughput and (b) 10% decrease in the target throughput.

To assess the impact of manipulating the throughput for the process in this case study the predicted RTDs at $\pm 10\%$ of the target throughput were used to reassess the impact of feeding variability and disturbances. Fig. 8 demonstrates the use of the RTD model in the risk assessment and evaluation of control strategies. At $\pm 10\%$ of the target throughput range, the impact is nearly the same for a disturbance of a given magnitude and duration in the feeder on the API concentration at the exit of the tablet press. There may be no additional risk to tablet uniformity from feeder fluctuations within the range of the throughputs that were examined in this case. As such, the feeder control strategy implemented at the target throughput may be suitable over the proposed throughput range for the process.

The predicted RTDs can also assist with the evaluation of the material diversion strategy at the higher and lower throughput if OOS product has been identified. The time for the OOS product to reach and clear the diversion point will of course be influenced by the change in the mean residence time. The amount of back-mixing in the process characterized by the RTD will also impact the extent of material to be isolated and rejected. The predicted RTDs were used at the lower and upper limits of the proposed throughput range to calculate when material diversion should start and end in the case of a large disturbance as shown in Fig. 9. From this plot, the times for which a product is OOS were found to be between 130 s and 141 s at the lower and upper limits of the proposed throughput range. This analysis could aid in determining how to establish an appropriate material diversion strategy over the throughput operating range for the process under consideration.

4. Conclusions

Utilizing published experimental data from continuous direct compression processes, dimensionless RTDs normalized by their respective mean residence time were found to be similar with throughput under certain operating conditions. The observed relationship can potentially

be used to predict the process dynamics at different throughputs for a give impeller rotation rate once the RTD is measured at the nominal operating point for the same rotation rate. To broaden the utility of this relationship, more validation work should be performed to examine whether this observed relationship remains over a wide range of different operating conditions (e.g., throughputs and impeller rotation rates), equipment, and formulations. Furthermore, the same validation work can be used to systemically examine the effect of impeller rotation rate on the dimensionless RTD. It is anticipated that this effort will enhance process understanding to extend empirically measured RTDs for solid oral continuous drug product manufacturing processes in a straightforward manner to aid in the development of a control strategy over a proposed range of operating conditions.

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