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ORIGINAL ARTICLE

Residence Time Distribution (RTD)-Based Control System for Continuous Pharmaceutical Manufacturing Process

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Abstract

Purpose During continuous manufacturing, there may be some out of specification tablets that need to be diverted in real time, in order to ensure the quality of the final product. Specifically, the content uniformity of each tablet must be guaranteed before it can be released to market. However, currently, no methods or tools are available that can assure the content uniformity and divert the non-confirming products in real time. The aim of this work is to develop and evaluate a strategy to divert the non-confirming tablets in real time and thereby assure drug concentration of final tablets.

Methods This work has been conducted in silico using a combination of MATLAB and Simulink. A methodology to implement a residence time distribution (RTD)-based control system for drug concentration-based tablet diversion which uses the convolution integral was developed and implemented in MATLAB. Comparisons between the performance of "fixed window" and "RTD-based" approaches for diversion have also been presented and used to assess optimal usability.

Results In this work, two novel strategies namely, "fixed window approach" and "RTD-based approach" have been developed and evaluated for real-time diversion of non-confirming tablets. The RTD-based control system was designed, developed, and implemented in silico. A framework for its implementation in a real-time system has also been elaborated on. This methodology was compared to an alternative fixed window approach. The proposed control system is analyzed for various manufacturing scenarios, systems, and disturbances.

Conclusions A comparison of the two proposed strategies suggests that the "RTD-based control system" is more efficient in every simulated scenario. The relative performance is best when the disturbances in the system are characterized by short pulse-like changes.

Keywords Residence time distribution · RTD · Control · Continuous manufacturing · Quality by design · Continuous pharmaceutical manufacturing

Introduction

The manufacturing route for pharmaceutical products in the industry is rapidly changing from batch to continuous with the latter picking up momentum due to its increased economic benefits and patient safety [1, 2]. The fact that a continuous process can be operated at steady state means that a complex control system can incorporated into its functioning for augmented process efficiency. Its involvement facilitates new and improved ways of controlling the process for optimal performance and also assists in better adhering to the regulatory constraints posed by the FDA [3]. Process automation and control has been developed and implemented in many cases [4–13]. These works, though based on control of important critical quality attributes (CQAs), do not mention any methodologies to deal with disturbance-affected product. Much less attention has been paid on diversion of out of spec tablets in real time which is essential for continuous pharmaceutical manufacturing [14]. This also means that there is currently no concrete industrialized methodology for out of spec product diversion. Therefore, the final product in the industry has to go through an offline testing step before it can be released and this increases the time it takes for the product to reach the market. Considering solid dosage manufacturing, the lack of an inline testing method inhibits the facilitation of manufacturing concepts like real-time release testing (RTRT), quality by control (QbC), and quality by design (QbD).

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In the context of direct compression as the manufacturing route, a process understanding is necessary in order to assure the product quality and adhere to the regulatory constraints proposed by the FDA. Such an understanding is capable of speeding up the process development stage and can also help generate better predictive models that can be used to develop control systems. Understanding the influence of disturbance propagation in the manufacturing system can assist in developing accurate models. On the one hand, the disturbances could be modeled and the control system can be tuned to deal with the process and on the other, disturbances that cannot be measured and modeled have to be dealt with by efficiently handling the affected product.

Within solid dosage manufacturing, upstream disturbances, caused by the feeding, milling, blending or formulation properties (example, agglomerated API), may propagate downstream to the compaction stage resulting in production of tablets that are out of spec. The feed frame in the tablet press, which feeds the powder into individual dies, is known to cause mixing in the incoming powder. To some extent, this mixing can reduce the magnitude of the disturbances. However, to deal with disturbances of higher magnitude other counter measures have to be put into place. Tablet presses currently possess the capability to reject tablets based on compression and ejection forces during production. The tablets produced during the startup phase can be also rejected. However, it does not have the capability to reject the tablets with an API concentration that has exceeded the pre-defined tolerance limits in real time. Currently, tablets are qualified through an offline concentration testing process postproduction. The offline testing procedure is time and resource intensive. Therefore, systematic methods and tools are needed for the purpose of real-time diversion of tablets violating drug concentration tolerance limits. This involves developing an inline tool that can reject or accept out of spec tablets based on a real-time prediction of the concentration.

The residence time distribution is a fundamental chemical engineering concept that is proposed in this context as a means to the real-time concentration based diversion methodology. By definition, it is the probability distribution of time that solid or fluid materials stay inside one or more unit operations in a continuous flow system. It can be used to characterize the mixing and flow behavior of material within a unit operation. In this work, the concept has been applied to a solid dosage continuous manufacturing process for the direct compaction route. Although, residence time distribution (RTD) has been traditionally applied to fluid systems, the characterization of powder flow has been the subject of many studies [15–17]. Prior reviews summarize the work that been done in the domain of unit operation characterization using RTD in chemical engineering domains and pharmaceutical solid unit operations respectively [7, 16]. The feed frame RTD model has been also reported in scientific literature [18]. As presented in previous literature, the use of the RTD in combination with an inlet concentration can provide a prediction of the outlet concentration [19]. This method has been used to develop and analyze an RTD-based control system, which predicts mean drug concentration of tablets, which subsequently determines the diversion periods.

This work presents a methodology to divert out of spec tablets based on the residence time distribution of the material in the unit operation for a specific system configuration. The RTD model in combination with an in silico diversion system has been used to analyze various scenarios in a continuous tablet manufacturing pilot plant. A framework for the implementation of this diversion system has also been presented. An alternative methodology called the "fixed window approach" which could be simpler to implement has been also developed. The proposed RTD-based tablet diversion methodology was compared with the fixed window methodology using manufacturing efficiency as a performance indicator.

The second section presents the process that this solution is aimed at. The proposed drug concentration-based real-time diversion strategy is presented in the third section. A brief description of RTD generation and its modeling has been presented after that in the fourth section. In the fifth section, the strategies for real-time assurance of tablet drug concentration have been described and an RTD-based control system has been developed. In the sixth section, a framework to assist in the implementation of the RTD-based control system has been elaborated on. The results are presented in the seventh section and finally, the manuscript is concluded in the eighth section.

Process Description

Continuous pharmaceutical manufacturing via direct compaction, wet granulation, and roller compaction is being increasingly adopted by pharmaceutical companies. A flexible continuous pharmaceutical tablet manufacturing process consisting of all of these manufacturing processes is shown in Fig. 1. The direct compaction (DC) route is the simplest and most economical manufacturing process. Roller compaction (RC) route is used when granulation of water-sensitive material is needed. This route is also known as dry granulation process. The wet granulation (WG) process is preferred when granulation of materials is needed before compaction. The proposed RTD-based control strategy is applicable for each of these manufacturing routes. The scenarios simulated in this work have assumed the direct compaction route one from Fig. 1. Such a direct compaction tablet manufacturing pilot plant has been installed and is situated at C-SOPS, Rutgers University, New Jersey, USA. The plant is built in three separate levels such that gravity can be used as the driving force for material transport. The top most level is assigned to powder storage and feeding, the middle layer is designated to the task of de-lumping and blending, and the bottom layer is used for compaction. Each of these levels spans an area of at least 100 ft^2. The current equipment set includes three gravimetric feeders with the capability of expansion. Following

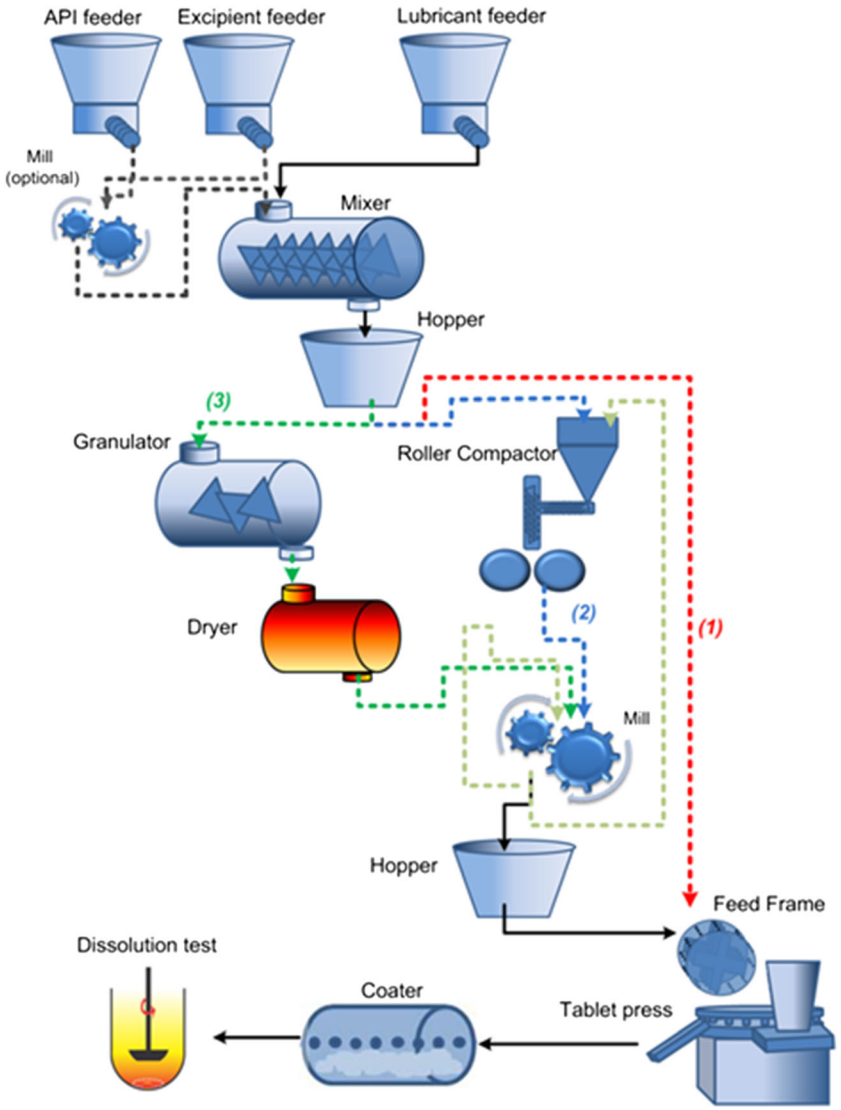

Fig. 1 Flexible continuous pharmaceutical tablet manufacturing process. (1) Via direct compaction. (2) Via roller compaction. (3) Via wet granulation

the feeders, a co-mill is integrated for de-lumping the powders as mentioned before and creating contact between the components. The lubricant feeder is added after the co-mill in order to prevent over lubrication of the formulation in the co-mill. All these streams are then connected to a continuous blender to create a homogenous mixture of all the ingredients. The exit stream from the blender is fed to the tablet press via a rotary feed frame. The powder blend fills a die, where the final compaction takes place. The tablets are then ejected out of the tablet press.

Drug Concentration-Based Real-Time Diversion Strategy

A drug concentration-based diversion system is desired for continuous pharmaceutical manufacturing. Conventional pharmaceutical manufacturing was based on batch processes, and therefore, such a system was not needed before. In a batch process, as seen in Fig. 2a, individual raw materials are mixed in a blender. The output from this is transferred into drums and is subsequently tested for content uniformity offline. If the product does not meet specifications, then entire batches may be disposed. Product that meets regulatory constraints is then stored and transported to the next unit operation. The feeder before tablet press may or may not be needed depending on specific plant setup. The final tablets are also stored in different batches and tested offline to assure CQAs. However, batch manufactcuring have several disadvantages including scaleup requirement, batch to batch variabilities in product quality, and lack of real time monitoring and control.

On the other hand, for the continuous manufacturing process, an upstream disturbance could propagate downstream if it has not been controlled locally or if the local control is not efficient causing overshoots. Depending on the performance of downstream unit operations, this disturbance could amplify or diminish. Nonetheless, due to this disturbance propagation,

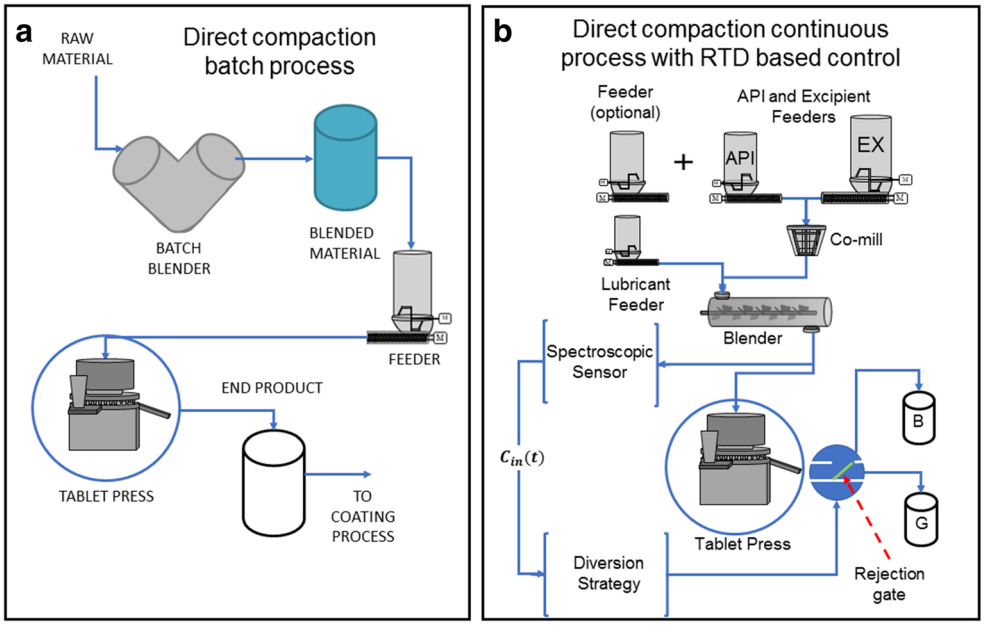

Fig. 2 Overview of drug concentration-based real-time diversion strategy. G, good tablet; B, bad tablet. **a** Direct compaction batch process. **b** Direct compaction continuous process with RTD-based control

there is a need to control or be able to mitigate situations that have the capacity to deteriorate end product quality. The steady-state operation of a continuous manufacturing process allows for the development of control systems as mentioned before. Drug concentration control as described in the following sections, although not traditional in the sense of control is a strategy that is desired as it reduces the need for offline testing post the compaction stage. It facilitates real-time release testing (RTRT) (if dissolution and other CQA's can be also assured in real time) as the tablets can then be seamlessly transported to the coating and packaging processes.

In Fig. 2b, such a "drug concentration-based diversion system" has been schematically illustrated. As shown in the figure, the blender is connected to the tablet press via a shoot that is designed to house process analytical technology (PAT) sensor. A spectroscopic device (NIR) is integrated here and data from this is collected and used for real-time monitoring of drug concentration. This creates a real-time availability of the inlet drug concentration data at the entry of the tablet press. The drug concentration-based control strategy developed in this work then uses this inlet concentration to determine a signal that can be used to reject tablets that are out of predefined tolerance limits at the outlet of the tablet press.

Residence Time Distribution Model

In this work, an RTD-based strategy is proposed to be applied for real-time tablet diversion. Prior to elaborating on the proposed strategy, the fundamentals of RTD have been introduced in this section.

RTD is the probability distribution of time that solid or fluid materials stay inside one or more unit operations in a continuous flow system. For a manufacturing plant or equipment, the RTD is a characteristic of the mixing that occurs inside it [20]. Typical chemical engineering jargon differentiates the RTD at the definitional stage using a continuous stirred tank reactor (CSTR) and plugged flow reactor (PFR) where the former exhibits a thorough mixing characteristic and the latter introduces a time delay.

For a system, the RTD may be derived by conducting tracer experiments. For a pulse experiment, once the inlet and the outlet concentration data is collected, the RTD function can be calculated as follows:

$$E_{\exp}(t) = \frac{c_{\text{out}}(t)}{\int_0^\infty c_{\text{out}}(t)dt} \tag{1}$$

where $E_{\exp}(t)$ is the experimentally obtained RTD and $c_{\text{out}}(t)$ is the outlet concentration with respect to time. This can be converted into the cumulative distribution function (CDF) ($F_{\exp}(t)$) using the following relation:

$$F_{\exp}(t) = \int_0^t E_{\exp}(t)dt \tag{2}$$

On the other hand, for a step change-based experiment, the following equation may be used to calculate the cumulative distribution function (CDF):

$$F_{\exp}(t) = \frac{C(t) - C_0}{C_f - C_0} \tag{3}$$

where C_0 is the inlet concentration before the step change, C_f is the inlet concentration after the step change, and $C(t)$ is the outlet concentration at time t. This can be converted into the RTD function using the following relation.

$$E_{\exp}(t) = \frac{dF_{\exp}(t)}{dt} \tag{4}$$

Additionally, from experimental data, the RTD can be characterized using the calculated mean residence time (τ) and variance (σ^2). These can be determined using the following equations:

$$\tau = \int_0^\infty tE(t)dt \tag{5}$$

$$\sigma^2 = \int_0^\infty (t-\tau)^2 E(t)dt \tag{6}$$

The increased involvement of RTD in the chemical engineering field has also led to the development of a myriad of models. The work has made use of the tank in series(T-I-S) model. The generalized model for tanks in series is given by the following equation:

$$E(t) = \frac{t^{n-1}}{(n-1)!\left(\frac{\tau}{n}\right)^n} e^{\left(\frac{-nt}{\tau}\right)} \tag{7}$$

where τ is the mean residence time and n is the number of continuous stirred tank reactors (CSTRs). Experimental data can be used to fit the parameters of this equation. Note that, the axial dispersion approach or any other methodology can be also use to develop the RTD model.

Strategies for Real-Time Assurance of Tablet Drug Concentration

The real-time diversion of tablets is challenging because there is currently no sensor available that can accurately measure the tablet potency and/or mean drug concentration of tablets in real time. However, the drug concentration of the blend can be measured in real time using well-established PAT techniques and tools [21]. Therefore, the tablet diversion method relies on "the real-time measurement of blend uniformity," "a model predicting tablet potency," and "the residence time from sensor's location to the tablet press outlet (diversion gate)." A systematic tablet diversion procedure is shown in Fig. 3. As shown, two approaches can be considered for tablet sorting based on drug concentration: a fixed window approach and a residence time distribution (RTD)-based approach. Both strategies need prior experimentation to identify the parameters required for implementation. However, the second approach (RTD based) may need relatively more complex experiments to be conducted when compared to the first approach. These concepts are further elaborated on in the subsequent sections.

Fixed Window Approach

Tablet diversion is facilitated using this approach through knowledge of time delays from the point of detection (chute or feed frame) to the point of the affect (tablet press outlet gate) in the system. The sensor that detects the concentration is connected to a comparator block which decides if the said concentration is within tolerance limits. If not, the experimentally derived time delay is applied and post this the diversion begins. The diversion stops when a concentration within spec is detected and another time delay is applied. These protocols can be represented using Eqs. (8) and (9). The time to start diversion can be calculated as follows.

$$t_r = t_o + t_{di} - \delta t \tag{8}$$

where $\boldsymbol{t_r}$ is the time at which diversion should start, $\boldsymbol{t_o}$ is the time at which the drug concentration of the blend goes out of its specifications, $\boldsymbol{t_{di}}$ is the time delay that the system requires to realize the change in concentration at the outlet, and $\boldsymbol{\delta t}$ is the safety margin to guarantee that no off spec tablets will be sorted in the good tablet lot. $\boldsymbol{t_o}$ can be obtained using real-time PAT sensor for blend uniformity measurement. $\boldsymbol{t_{di}}$ is predetermined using offline experimentations and it depends on both formulation and plant characteristics. It must be re-estimated if there are any changes in formulation and/or process conditions. $\boldsymbol{\delta t}$ is chosen by the operator based on experience working with the system.

The time to stop diversion can be calculated as follows:

$$t_a = t_s + t_{df} + \delta t \tag{9}$$

where t_a is the time at which diversion should stop, t_s is the time at which the drug concentration returns to an acceptable range, t_{df} is the time delay that the system requires to wash out the previous off spec materials. Like in Eq. (8), δt is the safety margin to guarantee that no off spec tablets will be sorted in the good tablet lot. t_{df} is similar to t_{di} and in most cases it is likely to be the same. Nonetheless, to avoid any assumptions, these are treated differently and it may be predetermined using offline experiments. Another reason to treat these values differently is that the system may behave differently for fluctuations in formulation and/or process conditions.

This concept is further illustrated in Fig. 4. As seen in the figure, for a pulse disturbance of unit magnitude from nine to ten, the diversion according to Eq. (8) begins at t_r and goes on until t_a. The diversion begins after the initial time delay, t_{di} has been applied and then lasts for the duration of the pulse disturbance. It then rejects tablets for another extended period of time governed by the value of t_{df}. Note that the RTD response shown in Fig. 4 is conceptual and has been used here for illustrative purposes. The RTD response depends on several factors including plant setup, operating parameters, formulation, etc. and must be re-estimated for each case.

RTD-Based Approach

In this methodology, the RTD of the system needs to be estimated through tracer experiments or any other suitable

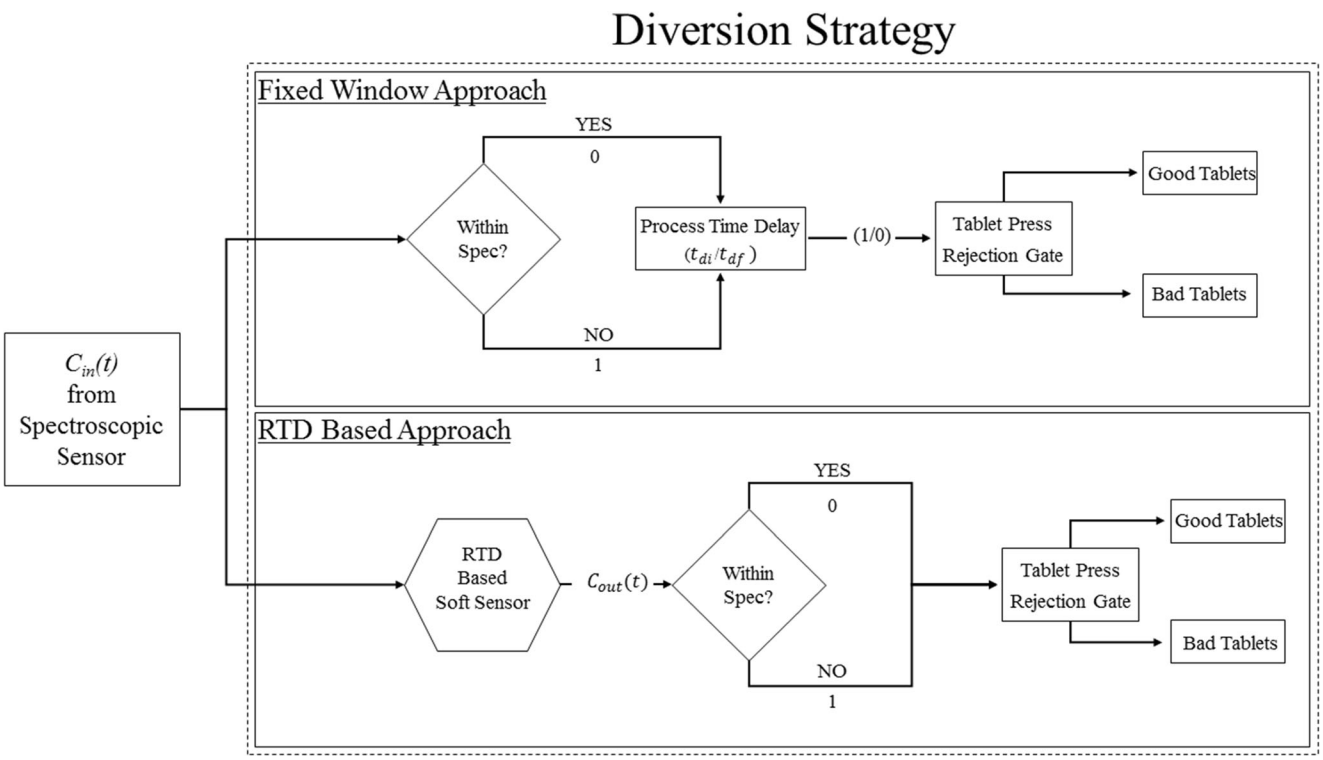

Fig. 3 Real-time diversion of pharmaceutical tablets. 0: accept, 1: reject

means. This estimated RTD can be used to predict the outlet concentration from the inlet concentration. The details of the implementation of the RTD-based diversion in Simulink are further illustrated in a later section in the

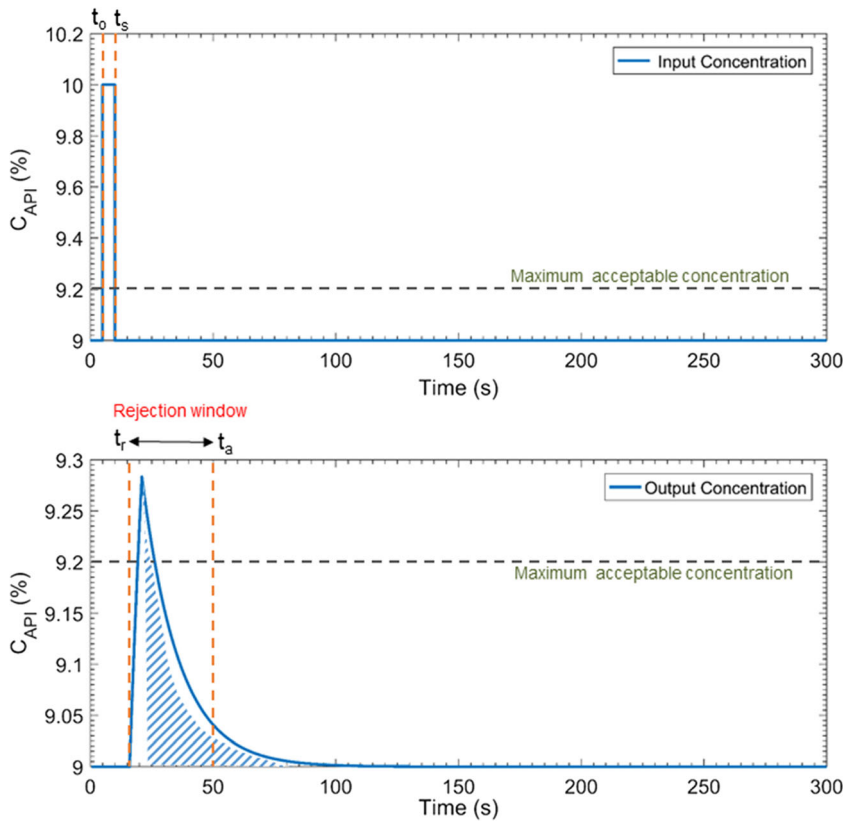

Fig. 4 Fixed window-based tablet diversion system

manuscript. The outlet concentration can be calculated using the convolution integral. Its shorthand representation is as follows:

$$C_{out}(t) = C_{in}(t) \times E(t) \tag{10}$$

where $C_{out}(t)$ is the outlet concentration, $C_{in}(t)$ is the inlet concentration, and $E(t)$ is the RTD of the system.

Using this relation, the outlet concentration can be predicted in real time and this signal can be used to initiate the diversion. One conceptual scenario is explored in Fig. 5, where a pulse disturbance is introduced in the system. The response in the system as predicted using the RTD shows a period where the concentration is out of specification. The diversion system which is dependent on the predicted signal rejects tablets only when the outlet concentration is out of specification. At this point a comparison can be made between the fixed window approach and the RTD-based approach. It is clear that the RTD-based approach sees a more accurate diversion of tablets. The improvement that the RTD-based approach provides is further explored in this paper.

An important consideration at this point is to note that the mean API concentration of the tablet is used to determine the diversion window as opposed to the potency. The reason for this lies in the dependency of the calculation potency on the tablet weight which at this point does not have many reliable real-time measurement methodologies.

Systematic Framework for Design, Evaluation, and Implementation of the RTD-Based Control System

Figure 6 shows a sequential framework that can be followed for the development and implementation of the RTD-based control system. Given that a residence time distribution characterizes the mixing within a unit operation and the time a fraction of material spends inside said operation, a change in the spatial characteristics, for example - change in reactor size or fill depth in the case of tablet compaction, would cause the RTD to be modified. The formulation characteristics can drastically change the flow behavior within the process. This too can modify the RTD of the system. From this, the reader may glean that the process parameters and the formulation must be kept constant in a system for the use of its RTD. Therefore, in the development of the RTD-based control strategy, a first step would be to accurately define the product, process, and plant configurations. The process should be run under operating conditions that are expected to be used in final manufacturing. Alternatively, one can develop a generic RTD model valid for a range of operating conditions and formulations. For the implementation of the control strategy, the RTD can be determined as mentioned in the "Residence Time Distribution Model" section. The illustrative formulation considered for this study consists of Excipient (89%), Lubricant (1%), and API (9%).

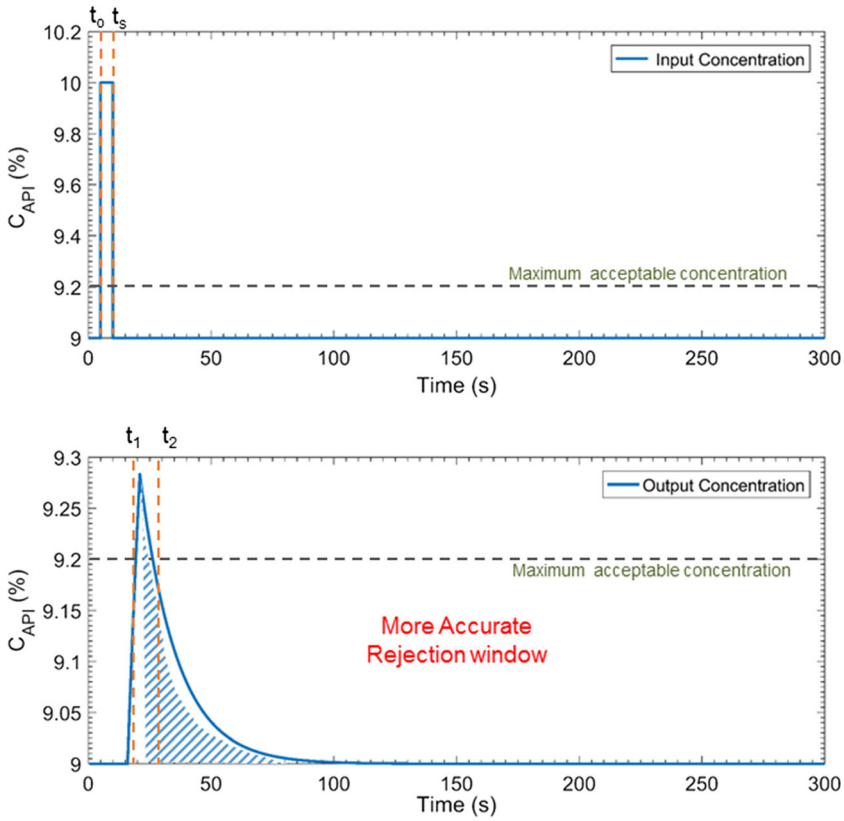

Fig. 5 RTD-based tablet diversion system

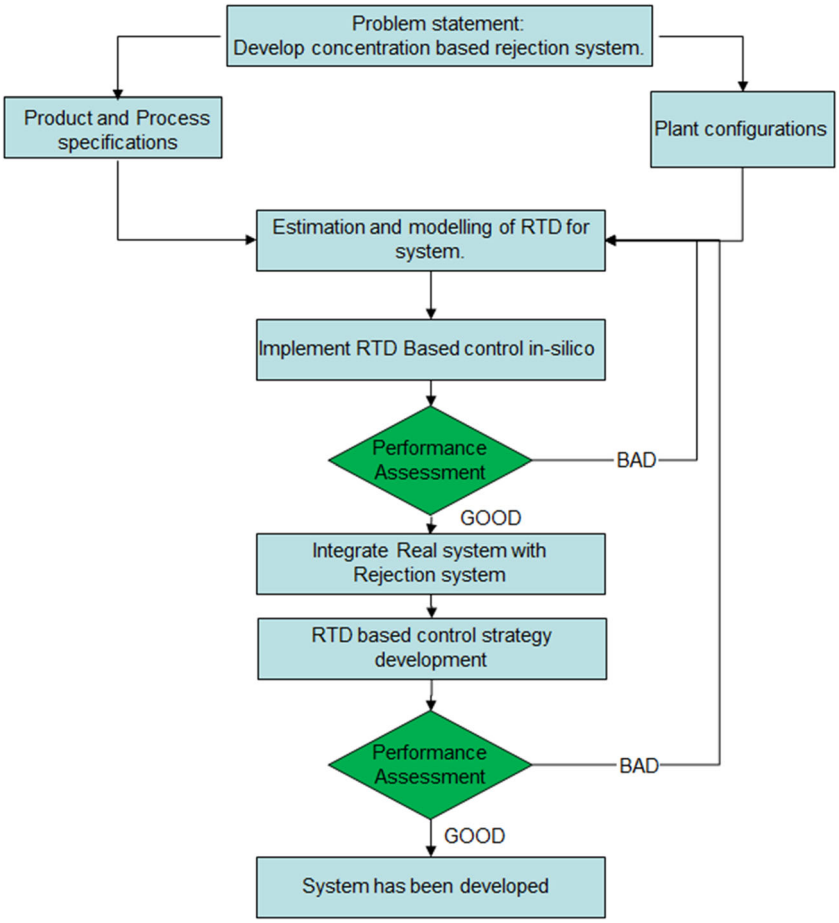

Fig. 6 Framework for design and implementation of RTD-based control system

Post RTD determination, the implementation of the prediction methodology is developed. For a linear system, a pulse or step response of a system at any time will behave and spread through the system just like a pulse of equal magnitude [18]. A measured input stream could be represented with a string of discrete values representing the fluctuations in the stream. Using the convolution integral for mixing, the final drug concentration can then be estimated. Using Eq. (10), it is possible to predict the outlet of a unit operation as long as the concentration of the inlet stream, $C_{in}(t)$, and the RTD, $E(t)$, are both known. The implementation of this equation in real-time system can be used to develop a prediction methodology where the inlet concentration of a blend is measured and the outlet concentration in a unit operation is predicted.

This convolution integral methodology can be implemented in silico with available process models. Various scenarios can be simulated and tested to analyze the control system. This manuscript, illustrates this step in detail as can be seen in the "Results and Discussion" section. The in silico analyses provides a tool for the implementation and development of a control strategy. This step is essential since it optimizes the use of expensive raw material and resources in the developmental stages. The performance of this strategy can be used to check for the accurateness of the RTD model. Additionally, performance metrics can also be developed and tested in silico. An example of a metric that can be used is the manufacturing efficiency as defined by Eq. (11).

$$\text{Manufacturing efficiency } (\varepsilon) = 100 \times \frac{\text{Good production}(t)}{\text{Total production } (t)} \quad (11)$$

A real-time analysis of the manufacturing efficiency can also be used to determine alarms in the control system. A production efficiency lower than a certain threshold can give process operators an indication of whether the production needs to be stopped to rectify any process faults.

Post the in silico design and performance assessment, the RTD model can be used in the plant for real-time tablet diversion based on mean API concentration. The implementation step essentially requires the integration of the plant with the diversion system and resolving all hardware and software connectivity issues. Validated PAT calibration models must also be developed for real-time drug concentration measurement. At this point, depending on the availability of materials, the system may be run for testing purposes. Performance issues that may arise at this stage can be attributed to inaccurate RTD

model identification and concentration detection methods. An iterative re-estimation of the RTD model using existing data set or new data sets can arrive at improved model.

In Silico Design of RTD-Based Control System

The RTD-based control system was developed and implemented using a combination of MATLAB and Simulink. The details of the implementation are elaborated on in this section.

Implementation of RTD Model for Prediction of Mean API Composition of Tablets

The cumulative distribution function of a unit operation from Eqs. (2) and (3) when normalized may be plotted on an *X*-axis and *Y*-axis where the maximum value on the *Y*-axis is one and the minimum value is zero. The *X*-axis may be extended as per the necessity to incorporate the full RTD function. Such a plot is shown in Fig. 7. The RTD model was implemented by entering a vector containing all the values from the *Y*-axis into the "finite impulse response block" in terms of their increments for a certain sampling time.

It was observed that the convolution integral from Eq. (10) could be calculated in real time by simply feeding the inlet concentration to the FIR block where the output signal is the convoluted outlet concentration. Figure 7 gives an illustration of this for a unit step response. A comparison of the output from the convolution integral and the output of the FIR block has been shown. As can be seen, the only difference lies in the step-like structure of the FIR response. This step-like structure can be attributed to the sample time which in this case is 1 s. It can be smoothened by using a smaller sample time. All the scenarios in this manuscript were generated using the FIR block as the RTD-based outlet concentration predictor.

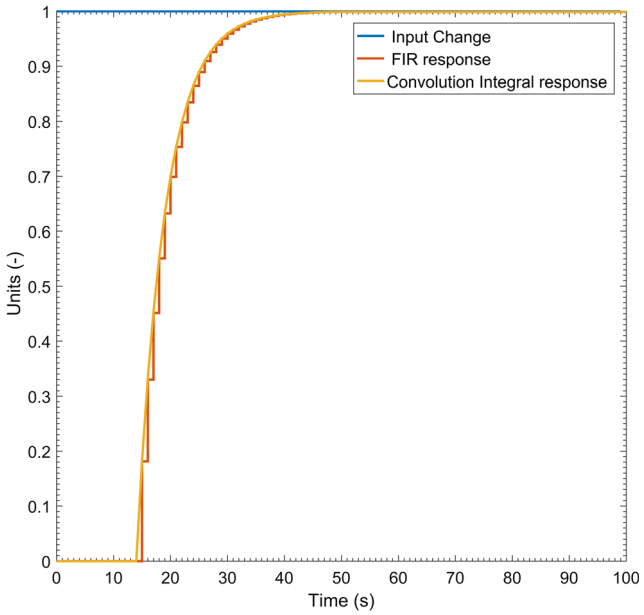

Fig. 7 Comparison of FIR response and convolution integral

Tablet Potency Prediction

Although, the proposed diversion system is based on mean API composition of the tablet, the potency has also been analyzed to demonstrate that it is also controlled using this control strategy. The potency calculation assumes that there is continuous real-time data for tablet weight. The potency is then calculated using the expression:

$$\text{Potency} = T(t) \times C_{\text{out}}(t) \tag{12}$$

where $T(t)$ is the weight of tablet produced continuously and $C_{\text{out}}(t)$ is the RTD-based prediction of the outlet drug concentration.

A methodology for real-time tablet weight measurement has been previously reported [4]. To simulate a signal similar to this, a band limited white noise block was used with parameters noise power = 0.0000000001, sample time = 2, and seed = 23,341. This signal is summed with a constant value of 0.4 g to simulate the real-time tablet weight $T(t)$ from Eq. (12).

Tablet Diversion System

The signal generated from the RTD concentration predictor (represented by the FIR block), that is, the predicted outlet concentration is fed to the diversion system. The diversion system is based on the difference between the reference mean API composition of tablet and the actual predicted concentration ($C_{\text{out}}(t)$). The absolute value of this difference is compared with an allowed tolerance which is pre-specified and normally dictated by regulators but was assumed in this case for conceptual demonstration purposes. This signal is fed to a relay block which produces a binary output signal (0, 1). This output is used to calculate diversion periods.

Results and Discussion

In this section, realistic scenarios were generated with both the RTD and fixed window-based control system. Both methodologies were compared in each scenario and its manufacturing efficiency was analyzed. These scenarios were evaluated based on potential manufacturing problems during continuous production. In each case, the disturbance has been introduced before entry into the tablet press and the affect is seen post compaction.

The evaluation has been presented for the rejection of positive pulse, step, and short positive step changes. The results for the simulation of disturbances in the negative direction mirrored those of the positive ones and therefore were not presented for the sake of brevity. The results for the manufacturing efficiency for both cases have been presented in Table 1.

The upper and lower limits used in these scenarios for the API concentration is assumed by the authors for the sake of conceptual demonstration. However, in practice, this value would be determined by the industry and regulators and could vary from formulation to formulation.

For the implementation of the fixed window approach, the time delay values (t_{di}, t_{df}) from Eqs. (8) and (9) were considered to be the same. It was approximated to be 200 s. This is the time taken to observe changes at the rejection gate of the tablet press where the input is the spectroscopic sensor at the inlet of the tablet press. The δt of Eqs. (8) and (9) are assumed to be zero in the case studies for demonstration purposes. This would be an experimentally derived parameter. The rest of the parameters used in the simulation study have been defined in Table 1.

Evaluation of RTD-Based Control System for Rejection of Pulse Disturbances

The API, which contains small particles with a tight size distribution, in some cases may agglomerate to larger granules. When the blending is not very efficient, agglomerated particles can cause sudden changes in the API concentration. Other reasons for such fluctuations can be if the feeder stops working for a short duration, a lump of API is introduced into the tablet press, the API feeder control overshoots, or its response time is faster or slower than the excipient feeder, etc. Nonetheless, such an occurrence can be treated as a disturbance and has been simulated in the form of a pulse disturbance. The case that has been presented consists of a positive pulse disturbance (high and low magnitude) as can be seen in Fig. 8. The disturbance was introduced at the hundredth second. It should also be noted that the initial 80s have been allotted to startup of the simulation.

Table 1 Parameters used for the simulation of the fixed window approach

Case study	t_r (s)		t_a (s)		δt (s)
	t_o (s)	t_{di}(s)	t_s(s)	t_{df}(s)	
1	1000	200	1005	200	0
2	1000	200	–	–	0
3	1000	200	1020	200	0

Case Study 1: Diversion of Tablets Caused by Positive Pulse Disturbances

In Fig. 8a, the output concentration spreads after a certain time delay and subsequently exceeds the acceptable range of both concentration and potency. The concentration and potency eventually return to the acceptable range once the effect of the disturbance has ceded. During this time period the production was analyzed and plotted. The RTD-based approach rejects tablets for a lesser time period and only when the actual predicted tablet concentration is out of range. In the case of the fixed window approach, the tablets are rejected for a slightly longer time duration.

Similarly, in Fig. 8b, the output concentration spreads and rises as an effect of the input pulse disturbance but does not exceed the boundaries at any time. The potency does not exceed the boundaries at any point as well. Therefore, the RTD-based diversion approach does not reject any tablets after the disturbance has been affected. According to the fixed window approach though, since it is dependent on the input concentration, there is a definite diversion period that follows the disturbance. The manufacturing efficiency is given in Table 2.

Evaluation of RTD-Based Control System for Rejecting Step Disturbances

In some situations, a feeder might start feeding more or less and this may go undetected. If the process monitoring system does not detect this, then another fail-safe measure would be to make use of the real-time diversion system at the tablet press outlet. This scenario has been simulated by a step change disturbance.

Case Study 2: Diversion of Tablets Caused by Step Disturbances

In Fig. 9, a step change disturbance has been simulated in the concentration to represent an excipient feeder that is feeding less. The resulting increase in the API concentration causes the potency to increase as well. The dynamics exhibited by this increase is derived from the RTD of the system. In both, the RTD-based approach and the fixed window approach, the diversion begins at around the same time and since the concentration does not return to the desired range, the system keep on diverting the tablets. On observing the graphs, it can be seen that there is little difference in the RTD-based approach and the fixed window approach. The manufacturing efficiency for the RTD-based approach is only 2% more than the fixed window-based approach as given in Table 2.

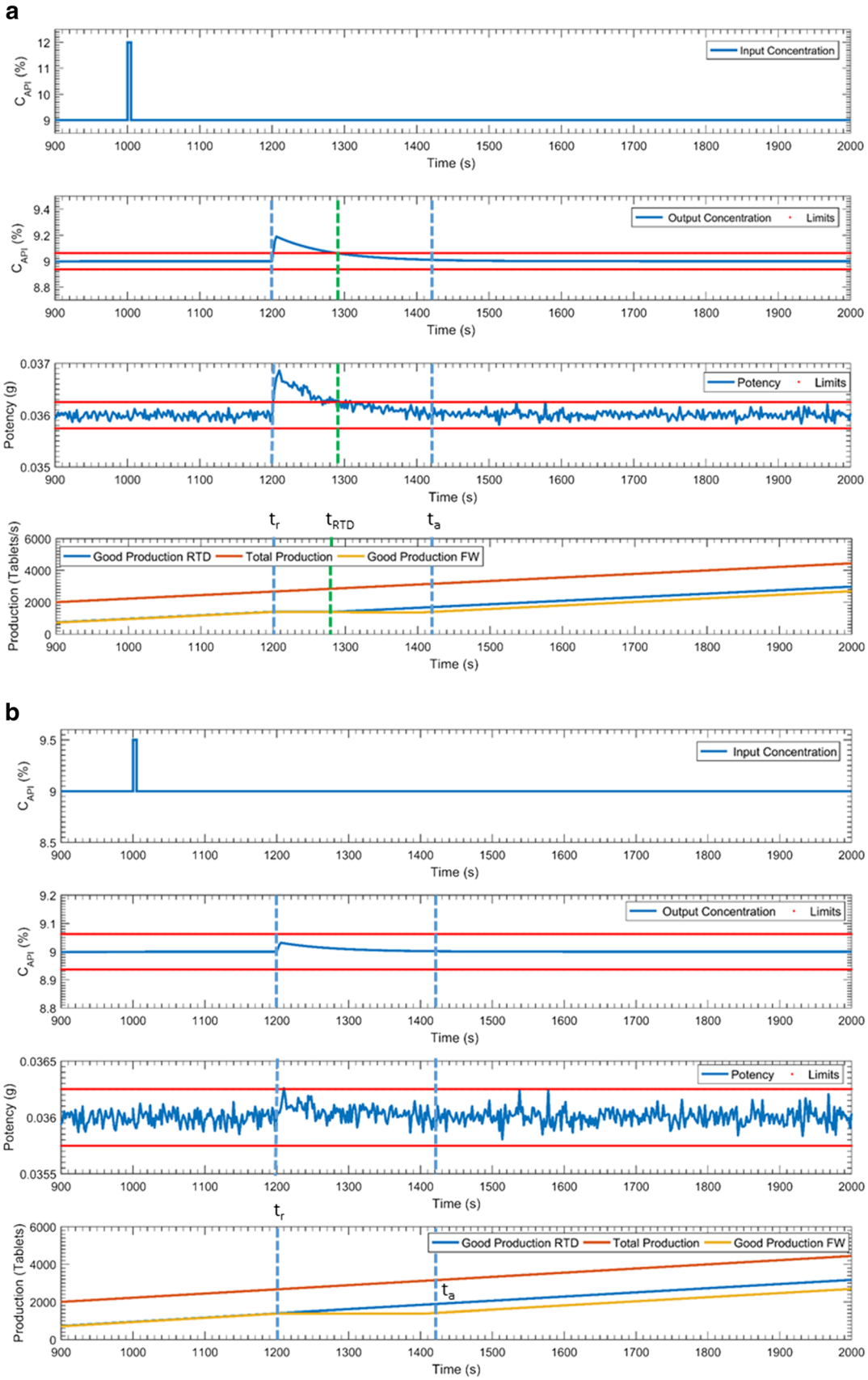

Fig. 8 Fluctuation in API concentration. **a** High magnitude. **b** Low magnitude

Table 2 Manufacturing efficiencies of case studies 1–3

Scenario		Magnitude	Manufacturing efficiency, ε (%)	
			RTD	Fixed window
Pulse disturbances	Case study 1	High	94.6667	87.1667
		Low	100	87.1667
	Negative pulse	High	94.6667	87.1667
		Low	100	87.1667
Step disturbances	Case study 2	NA	71	69
	Negative step	NA	71	69
Short step disturbances	Case study 3	High	72	71
		Low	79	71
	Negative short step	High	72	71
		Low	79	71

Evaluation of RTD-Based Control System for Rejecting Short Step Change Disturbances

In some situations, compacted and badly mixed API can result in disturbances that may last more than a few seconds and subside once the material passes. This has been simulated in Fig. 10 with two magnitudes. The degree to which powder is compacted can result in a high- or low-magnitude disturbance.

Case Study 3: Diversion of More Potent Tablets Caused by Short Positive Step Disturbances

In Fig. 10a, the disturbance is of a higher magnitude and lasts 20 s. The output concentration response and potency as predicted is shown and this exceeds the tolerance. The result of this is a diversion as seen in the plot. The fixed window approach and the RTD-based approach provide very similar results in this case but the latter provides a 1% improvement.

In Fig. 10b, the disturbance lasts for 20 s as well but the magnitude is much lesser. The concentration and potency exceed the toleration limits and subsequently diversion begins in both the RTD-based approach and the fixed window-based approach. In this case, the decreased magnitude of the disturbance results in the improved performance of the RTD-based approach.

Evaluation of RTD-Based Control System for Rejecting Random Disturbances

In the pharmaceutical industry, real-time concentration is measured using NIR, RAMAN, and other spectroscopic devices.

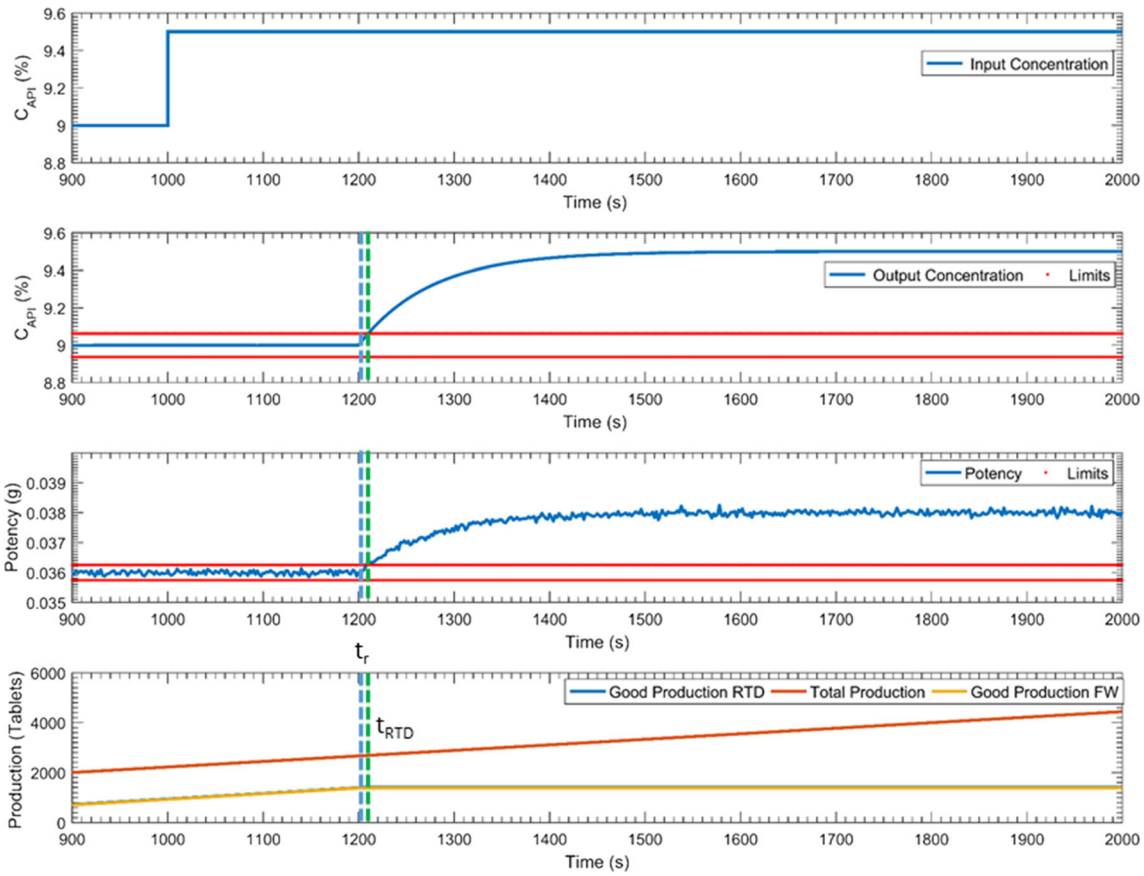

Fig. 9 Positive step disturbance

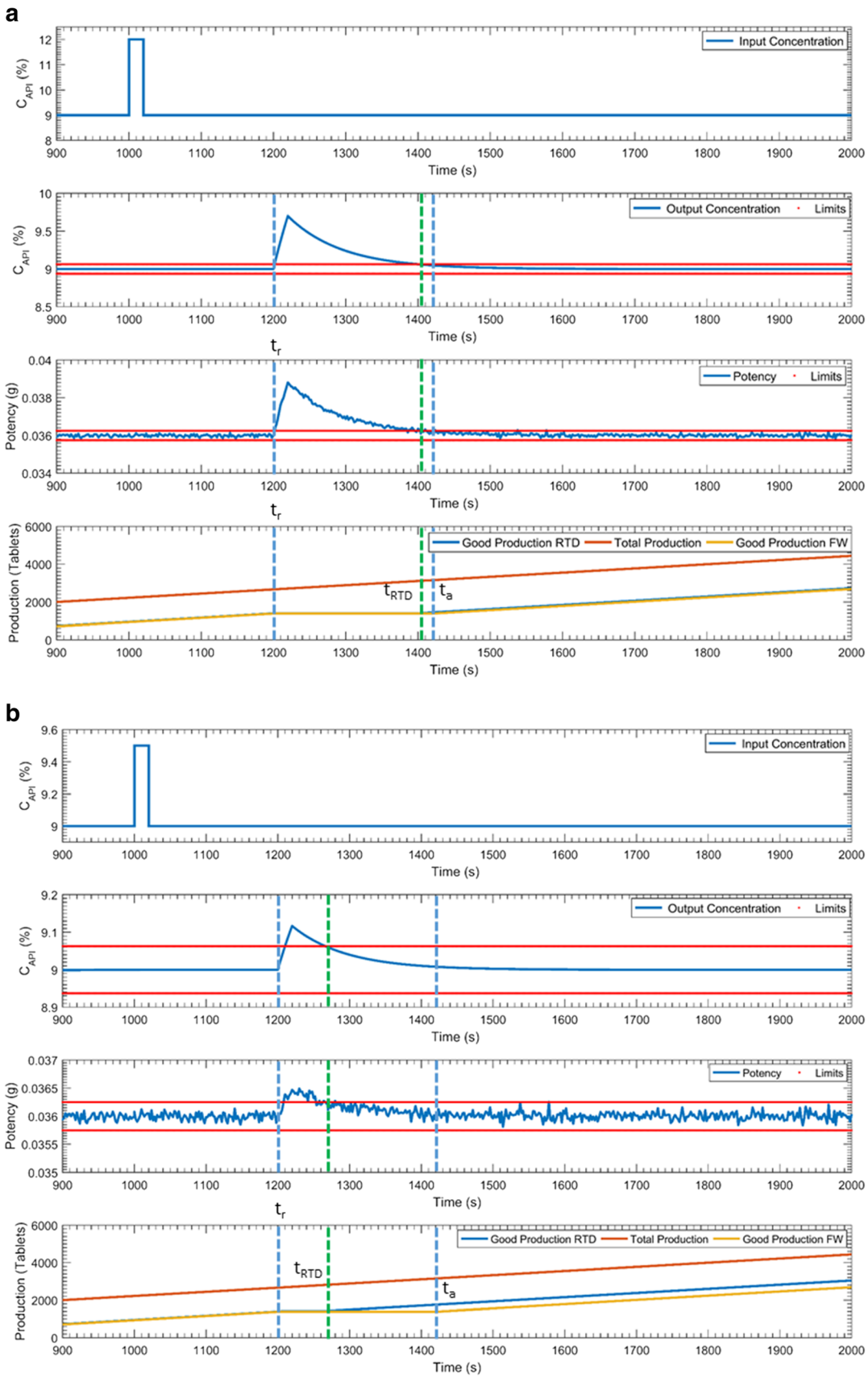

Fig. 10 Short positive offset in concentration. **a** High magnitude. **b** Low magnitude

These devices rely on the collection of spectra inline and PAT models for their concentration prediction. It is possible that for short periods of time, there is a high fluctuation in the inlet concentration. Even if the powder is uniformly mixed, it is possible that the concentration varies continuously in magnitude around a certain mean. Such a signal has been simulated in Fig. 11. Here, the input concentration fluctuates constantly and violates the boundaries. In such a situation, since the fixed window approach is dependent on the input signal, it would initiate diversion. Since there is a violation of the boundaries at multiple time points, there would subsequently be more diversions initiated. This would detrimentally affect manufacturing efficiency since all tablets rejected during this period as seen from the calculated output concentration are within the allowed limits almost throughout the entire timespan of simulation except at the one hundred and sixtieth second (Table 2). This means that there would be unnecessary diversion by the fixed window strategy. On the other hand, the RTD-based control strategy would reject tablets only during the brief period that there is a violation.

Performance Assessment of RTD-Based Control System for Different Processes

The proposed RTD-based control system is process dependent and must be re-tuned for different processes. In this section, the RTD-based control strategy has been evaluated for different processes. The different processes have been simulated via varying number of tanks in the 'tank in series model' with a plug flow reactor to simulate the delay in the response. The justification for this consideration is to show that the prediction of the outlet concentration can be drastically different in different systems and the performance may vary based on the system. In Fig. 12, the outlet concentration has been plotted for 1, 5, 10, and 15 tanks. With an increase in the number of tanks, the spread of the response widens and the effect of the disturbance persists in the system for much longer. Subsequently, the diversion times increase with the number of tanks.

Conclusions

In this work, an RTD-based control system was designed, developed, and implemented in silico. This methodology was compared to an alternative fixed window methodology. In the fixed window methodology, process time delays are applied to determine diversion periods while in the RTD-based strategy, the predicted outlet concentration determines the diversion window. From the results, it was observed that the RTD-based approach performed better than the fixed window-based approach in all cases. This was reinforced by the calculated manufacturing

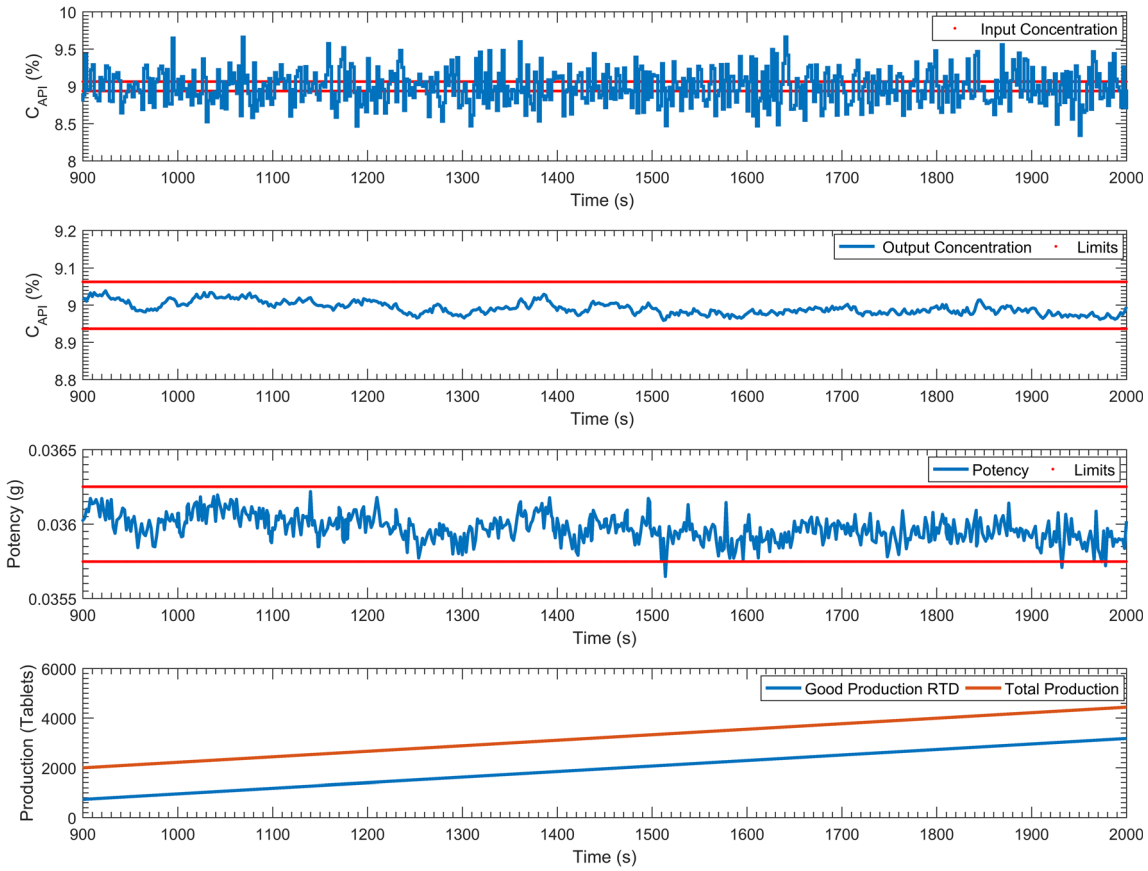

Fig. 11 RTD-based control simulated for a noisy input concentration data

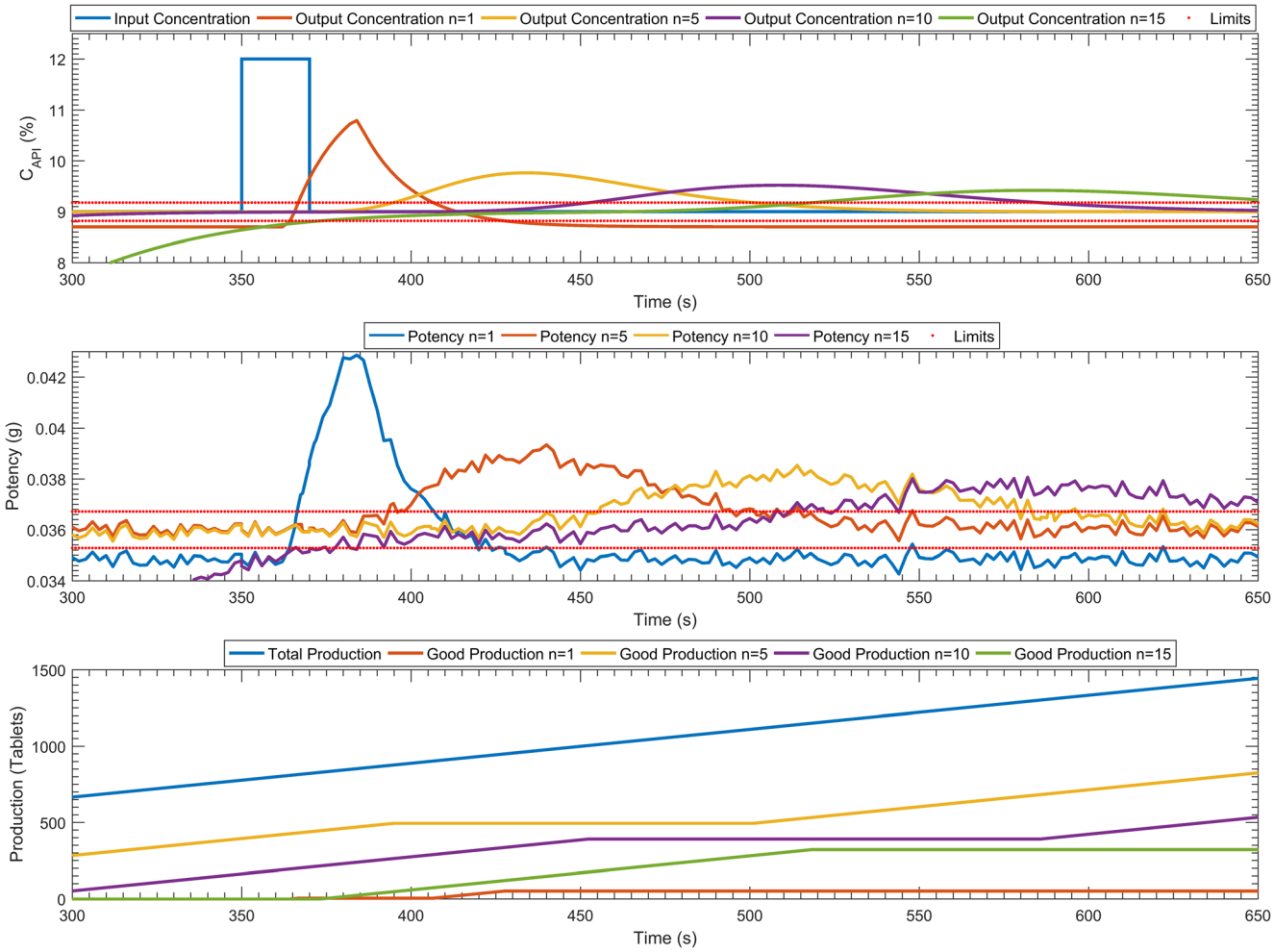

Fig. 12 Performance assessment of RTD-based control with different RTD models

efficiency presented in Table 2, which was used as a metric to quantify the improvement. The magnitude of improvement varies depending on the size and type of disturbance. If the disturbance is long and step like, then the methodology that is easier to implement may be chosen. However, when the disturbance is characterized by short pulses, the RTD-based diversion strategy, due to its augmented performance should be chosen.

It should be noted that during the startup phase, the tablets are diverted to ensure the product quality. Therefore, the total cumulative production will always be more than the good tablet production. This scenario has been also simulated in the presented case studies. During simulation, there is a brief rejection period at the start in both the fixed and RTD-based approach since the simulation of the output concentration starts from zero and then reaches steady state. This causes the offset in the graphs. This rejection period was omitted from the manufacturing efficiency calculation and therefore does not influence the results.

Additionally, accurate measurements are necessary for the optimal performance of any control strategy. Therefore, the RTD of the system and its corresponding model needs to be developed very carefully. The performance of the RTD-based control system will be as good as the accuracy of the RTD model. The results will be highly sensitive to mismatches between the actual RTD and modeled RTD. Safety margins can be used to take into account mismatches between the model and the plant. The range of variation of the RTD prediction that could be accepted depends on the acceptable limits of drug concentration variation imposed by regulators for a particular product.

The developed system's application is directed mainly towards continuous pharmaceutical manufacturing processes where it can facilitate more efficiency in production. This, however, does not restrict its use to a direct compaction continuous pharmaceutical line. It can be adapted and used in any continuous processes. The future work includes the implementation of RTD-based control strategy into the pilot plant facility.

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Appendix

Nomenclature

Abbreviations	Variable
API	Active pharmaceutical ingredient
CSTR	Continuous stirred tank reactor
CQA	Critical quality attributes
NIR	Near infrared
PFR	Plugged flow reactor
PAT	Process analytical technology
RTRT	Real-time release testing
RTD	Residence time distribution

Symbol	Variable	Units
C	Concentration	g/m^3
$C(t)$	Concentration at time t	(%)
$E(t)$	Residence time distribution function	s^{-1}
$F(t)$	Cumulative distribution function	(−)
n	Number of tanks	(−)
t	Time	s
ε	Manufacturing efficiency	%
σ	Variance	s
τ	Mean residence time	s

Subscript	Variable
a	Accept
di	Initial delay
df	Final delay
exp	Experimental
f	Concentration after step change
in	Input stream
o	Off-specification
out	Output stream
s	Specification
r	Reject

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