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Control strategy and methods for continuous direct compression processes

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\textbf{A B S T R A C T}

We presented a control strategy for tablet manufacturing processes based on continuous direct compression. The work was conducted by the experts of pharmaceutical companies, machine suppliers, academia, and regulatory authority in Japan. Among different items in the process, the component ratio and blended powder content were selected as the items requiring the control method specific to continuous manufacturing different from the conventional batch manufacturing. The control and management of the Loss in Weight (LIW) feeder were deemed the most important, and the Residence Time Distribution (RTD) model were regarded effective for setting the control range and for controlling of the LIW feeder. Based on these ideas, the concept of process control using RTD was summarized.
1. Introduction

In the last years, continuous manufacturing has been implemented in the commercial production of solid drug products. In 2018, the first approval was given for continuous manufacturing in Japan, which was based on direct compression process. Typically, direct compression process consists of three steps: raw material blending, tableting, and coating. These steps are interconnected in continuous processes, so that the raw materials are fed into the process, and the tablets are obtained from the process simultaneously.

The understanding of continuous direct compression is growing along with the increased presence of the technology. One topic often found in the literature is monitoring and control. Pawar et al. [1] applied near infrared (NIR) prediction of dissolution of tablets made by continuous direct compression towards real time release testing (RTTR). De Leersnyder et al. [2] developed an in-line NIR spectroscopic method for continuous blend potency determination in the feed frame of a tablet press. Almaya et al. [3] presented a control strategies of the process with a focus on the state of control, product collection, and startup/shutdown operations for clinical and commercial production. Moreno et al. [4] investigated sensor network robustness using model-based data reconciliation. Another well-investigated topic is quality variation measured by the residence time distribution (RTD). Van Snick et al. [5] applied inline NIRS to estimate the RTD in the mixer and to monitor blend uniformity for producing sustained release tablets. Escotet-Espinoza et al. [6] analyzed the effect of tracer material properties on the RTD in the blending step of the process. Bhaskar et al. [7] reported an RTD-based control system where non-conforming materials were diverted on a real time basis. Billups et al. [8] used RTD for analyzing material traceability for determining raw material batch changes. Besides, the role of continuous manufacturing and continuous direct compression processes has been analyzed from quality and economic perspectives [9-11].

Regulatory authorities, as the backbone to provide quality products to the patients, have been recognizing the relevance of continuous manufacturing including direct compression processes. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) documentations provided ICH Q8 (R2) [12], Q9 [13], Q10 [14], Q11 [15], and Q12 [16] as the basis for adopting Quality-by-Design (QbD) approaches. From November 2018, activities have been carried out toward the development of a new guideline for continuous manufacturing as ICH Q13 [17]. Currently, each regulatory authority is working on the issues to apply the current regulations for continuous manufacturing based on the batch manufacturing method in parallel with the discussion in ICH Q13. From 2016 to 2018, a Japan Agency for Medical Research and Development (AMED) research project was performed on a “Research into Quality Assurance of Pharmaceutical Continuous Manufacturing”. The project was led by the author Yoshihiro Matsuda in Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese regulatory agency. As the outcomes, “Points to Consider Regarding Continuous Manufacturing” Document [18] was first published in March 2017. Then “State of Control in Continuous Pharmaceutical Manufacturing”, an important concept in continuous manufacturing [19], was published in March 2018. These documents summarize the opinions of experts in industry, regulatory authority and academia on the concept to take actions to consolidate the environment where companies may easily apply continuous manufacturing.

In the fiscal year 2018, a new AMED project started for the “Study on Quality Assurance of Pharmaceutical Continuous Manufacturing”, where the authors of the present paper are participating in this project with Yoshihiro Matsuda as the project leader. In order to promote continuous manufacturing in Japan, we have been conducting activities to present the measures to ensure the state of control in the process as well as the effective control methods to ensure the product quality. This time, we generally focused on process control, and summarized tools and points to consider for manufacturing control. For the continuous direct compression processes, RTD models were investigated particularly as a useful tool for process control.

Based on these activities, we present a control strategy of continuous direct compression processes. The paper first introduces the overview of the target process, followed by the items to be controlled in the process and the setting of the control range using RTD model. The presented contents were discussed and agreed by the experts from drug producers, machine suppliers, academia, and the Japanese regulatory authority, PMDA, which is the originality of the work. Thus, the presented contents can serve as a solid fundament for adopting a new control method of continuous direct compression in and beyond the Japanese market.

2. Target process

In the continuous direct compression process investigated in this study, as shown in Fig. 1, the raw materials including the active pharmaceutical ingredient (API) are continuously supplied to Blender 1 by the Loss in Weight (LIW) feeder, and they are mixed by Blender 1 (Blending process 1). Then, the blended powder is transferred to Blender 2, and at the same time, external additives such as lubricant are supplied to
Blender 2 by a LIW feeder and mixed (Blending process 2). The blended powder for tableting was transferred to a tablet press to make tablets (Tableting process), and the tablets are coated by a small amount of sub-batch using a semi-continuous film coating machine (Coating process). The characteristics of this process are as follows: the raw materials are supplied continuously by LIW feeders, the materials continue to move from the upstream process to the downstream process without remaining in the process, and they are formulated as a bulk drug product.

3. Items to be controlled in the process in continuous direct compression

3.1. Selection of the items to be controlled in the process

The continuous direct compression process has process parameters and material attributes that are specific to continuous manufacturing and must be controlled since raw materials and intermediate products continuously move in the process. The items to be controlled in the continuous direct compression process were discussed, focusing on the significant difference of operations between continuous manufacturing and batch manufacturing. As a result, the LIW feeding operation was selected as an item to be controlled. The LIW feeding operation, which corresponds to the weighing process in batch manufacturing, determines the component ratio of the drug product and affects the critical quality attributes (CQAs) of the drug product (i.e., assay and content uniformity of dosage units) via the blended powder content. Thus, control of LIW feeders is crucial in the continuous direct compression process. The differences between batch and continuous manufacturing for the component ratio and blended powder content are shown in Table 1.

3.2. Process control

3.2.1. Process variability to be considered for in-process control

In the continuous direct compression process, there are three types of typical variation patterns of process parameters and material attributes to be controlled. Table 2 shows such variation patterns and corresponding control methods. Since the actual variation may be a combination of these variation patterns, it is important to consider all of these variation patterns when developing control methods of the LIW feeders.

3.2.2. Concepts for control in continuous direct compression

In order to control the component ratio and the blended powder content in the continuous direct compression process, it is necessary to monitor the manufacturing state and control the process parameters to the target values/set values. Depending on the state, it is necessary to judge whether it should be treated as a conforming product, whether it should be diverted from the process as a defective product, or whether equipment or quality should be checked by stopping the equipment. Table 3 summarizes the concept of what tools are useful for monitoring and control and how to manage the process.

[Control of component ratio]

Each material is consistently monitored and controlled to a target feeding rate by an independent LIW feeder. In the component ratio control, it is most important to control the feed rate of each LIW feeder so that it becomes the set value and consequently the component ratio becomes the target value as shown in No. 1 in Table 3. If the LIW feeding rate of each component is within an appropriate acceptance value/range (upper and lower limits), the component is judged as a conforming article. If it exceeds the acceptance value/range, judgment such as diversion from the system or shutdown of the equipment is made.
**Table 1 – Differences between batch and continuous direct compression methods for the component ratio and blended powder content.**

| Manufacturing method | Batch direct compression | Continuous direct compression |
|----------------------|--------------------------|------------------------------|
| Component ratio (Unit formula) | Weigh a predetermined amount of raw materials for 1 batch and charge in the whole amount. Variability of blended powder content between sampling points in the blending container. | Charge in each raw material continuously using the LIW feeders. Change in blended powder content over time. |
| Blended powder content (blend uniformity) | | |

**Table 2 – Possible variation patterns of continuous direct compression process.**

| Variation pattern | Variable content | Control |
|-------------------|------------------|---------|
| 1. Temporal | PP/MA* to be controlled | The process parameters or material attributes to be controlled increase or decrease with a certain trend. If there is no control, the value of process parameters or material attributes outside the acceptable range after a certain time. Monitor the process parameters or material attributes to be controlled and change the parameter values towards set values/target values. |
| 2. Variability | PP/MA* to be controlled | The process parameter or material attribute to be controlled varies up and down. If there is no control, it often goes beyond the acceptable range. Monitor the process parameters or material attributes to be controlled and change the parameter values to reduce variability towards set values/target values. |
| 3. Transient | PP/MA* to be controlled | The process parameters or material attributes to be controlled temporarily increase or decrease due to disturbance. The process returns to its original state even if there is no control. The process parameters or material attributes to be controlled are monitored, but the intended control is not possible because they return to the original state in a short time. |

*Process Parameters / Material Attributes.*

It is appropriate to judge diversion from the system or equipment shutdown, considering the variations shown in Table 2. Even if fluctuations due to disturbances occur, stable manufacturing can be achieved by continuously monitoring the process states and suppressing the fluctuations through feedback/feedforward control. When a disturbance is larger or more frequent than assumed and the component ratio exceeds the upper or lower limit, diversion may be performed to avoid the impact on the process if the disturbance is temporary. However, in cases where the magnitude or frequency of the disturbance exceeds the capability of the process control, it is desirable to shut down the equipment rather than diversion. Equipment shutdown is appropriate when the control is not working normally, for example, when a diversion from the system continues in variation pattern 1, when it frequently occurs in variation pattern 2, or when considerable variation occurs in variation pattern 3.

No. 2 in Table 3 is to control the feed rate so that, for example, the excipient is supplied at a preset ratio against the API in accordance with the variation in the feed rate of the API, assuming that No. 1 mentioned above is controlled. However, this control method is difficult to apply when the process parameters or material attributes to be controlled repeatedly move up and down, like variation pattern 2 in Table 2. Therefore, the control of No. 2 is considered to be useful as an auxiliary control of No. 1.

The method shown in No. 3 in Table 3 directly measures the concentration of components using NIR, Raman, etc. They are not used to control each component’s feed rate because the LIW feeder controls it. Instead, the NIR, Raman, etc. are used to detect process abnormalities in advance and to make decisions such as diversion from the system or shutdown of equipment, as a tool to support the control of the LIW feeder. Also, they are beneficial to acquire knowledge of time-series variation of each ingredient in the development stage and deepen the understanding of the process by using them for preparation and verification of the RTD model.

[Control of blended powder content]

The blended powder content is controlled by the LIW feeder similarly to the component ratio control, under the assumption that the blending process uniformly blends each component. Therefore, the proven acceptable ranges (PARs) and design space (DS) for the critical process parameters (CPPs) of the blending process are established in the development stage, and the blended powder content is controlled by the LIW feeder while controlling the
### Table 3 – Concepts for control in continuous direct compression.

| CMA No. | Control by equipment Monitor | Control | Process control Conforming product | Diversion | Shutdown |
|---------|-------------------------------|---------|---------------------------------|-----------|---------|
| Component ratio (Unit formula) 1 | Monitor the feed rate with the LIW feeder. | Control the LIW feed rate to the set value. | The measured value of the feed rate is within the acceptance value. The RTD model, etc. can be used to set the acceptance value. | If the measured value of the feed rate exceeds the acceptance value, divert it using the RTD model, etc. | • Diversion continues for a certain period of time. • Diversion occurs frequently. • The degree of abnormality is large. |
| 2 | Monitor the feed rate with the LIW feeder. | Calculate each component ratio from the value of the LIW feeder and control the feed rate so that the ratio is kept as a constant. | The component ratio is within the acceptance value. | If the component ratio exceeds the acceptance value, divert it using the RTD model, etc. | • Diversion continues for a certain period of time. • Diversion occurs frequently. • The degree of abnormality is large. |
| 3 | Monitor the content of each component by NIR/Raman. | – | The measured value of the feed rate is within the acceptance value, and the NIR/Raman measurement result is within the acceptance value. | If the NIR/Raman measurement result exceeds the acceptance value, divert it using the RTD model, etc. | • Diversion continues for a certain period of time. • Diversion occurs frequently. • The degree of abnormality is large. • Shut down when NIR/Raman failure is detected. |
| Blended powder content (Blend uniformity) 4 | – | Control the process parameters within PARs or DS. | Process parameters are within PARs or DS. | If process parameters are out of the range of PARs or DS, divert it using the RTD model, etc. | • Diversion continues for a certain period of time. • Diversion occurs frequently. • The degree of abnormality is large. • Shut down when NIR/Raman failure is detected. |
| 5 | Monitor the API content by NIR/Raman. | – | The process parameters are within PARs or DS, and the NIR/Raman measurement result is within the acceptance value. | If the process parameters are within PARs or DS but the NIR/Raman measurement result exceeds the acceptance value, divert it using the RTD model, etc. | • Diversion continues for a certain period of time. • Diversion occurs frequently. • The degree of abnormality is large. • Shut down when NIR/Raman failure is detected. |
CPPs within the established PARs and DS. When the LIW feeder is controlled within the acceptance value/range, the intermediate product is regarded as conforming if the process parameters of the blending process are within PARs and DS, and a judgment of diversion from the system or equipment shutdown should be made if they exceed the PARs and DS. The same concept as in the component ratio control applies to the decision on equipment shutdown. Monitoring and process control using NIR and Raman are of the concept similar to the control of the component ratio.

4. Setting of the control range of the LIW feeder using the RTD model

4.1. What is the RTD model?

The RTD model is a well-known theory in reaction engineering and can provide information about material flow and component concentration within the reactor. In the continuous direct compression process, the RTD model enhances the understanding of how the API and each excipient component flow in the blender and how they are blended; thus, it has been investigated as an important tool for process understanding and control. There are three major types of RTD models: plug flow reactor (PFR), continuous stirred tank reactor (CSTR), and laminar flow reactor (LFR). In the continuous direct compression process, PFR and CSTR shown in Table 4 and Fig. 2, as well as a model combining both (Conversion model) can be used.

If a blender or a stirring feeder is modeled by one PFR and two CSTRs, the relationship between the concentration at the inlet \( (C_{\text{in}}) \) and the concentration at the outlet \( (C) \) is expressed by Eq. 1 based on mass balance. Where \( \theta, t_1, \) and \( t_2 \) represent the lag time and the average residence time of the first and second CSTR, respectively, which are the specific parameters of the equipment.

\[
C_{\text{in}}(t - \theta) = C(t) + t_1 \frac{dC(t)}{dt} + t_2 \frac{d^2C(t)}{dt^2} + t_1 t_2 \frac{d^2C(t)}{dt^2} \tag{1}
\]

The RTD model is a function, which depends on the size of the equipment, blending conditions, powder fill level in the equipment, and powder feed rate, and it is not affected by variations in environmental conditions such as temperature and humidity in the production room.

| Model             | Description                                                                 |
|-------------------|-----------------------------------------------------------------------------|
| PFR               | No flow axial blending occurs and all particles have the same residence time. Follow the first-in first-out principle. |
| CSTR              | All components are blended instantly. Concentration changes are expressed as exponential functions. |
| Conversion model  | Combination of PFR and CSTR. The actual blending state is represented by the delay time by PFR and multiple CSTRs. |

4.2. How to develop the RTD model

The RTD model parameters \( (\theta, t_1, \) and \( t_2) \) can be determined by fitting them with the actual concentration of the API or tracer measured continuously by in-line NIR, etc. Representative examples of how to develop the RTD models include an impulse response test (spike test), a step response test, and a multistep response test (relay tests) as shown in Table 5. All the methods are available for developing an RTD model of the continuous direct compression process. However, in actual application, it is necessary to select an optimal method according to the formulation, process, and so forth.

Fig. 3 is an example of an RTD model of a continuous blending process, constructed from an impulse response test, in which a tracer was added from the inlet of Blender 2, and the tracer concentration was measured by NIR placed between the Blender 2 and the tablet press force feeder. By obtaining the parameters \( \theta, t_1, \) and \( t_2 \) that minimize the difference between actual NIR data and the predicted values from the RTD model, the delay time of Blender 2 and the change in concentration in the blender can be calculated. By determining RTD parameters of Blender 1 and force feeder in a similar manner and integrating them, it becomes possible to grasp the changes in concentration throughout the process.

4.3. Process control using the RTD model

In the continuous direct compression process, the process variation caused by the LIW feeder is transmitted to the tablet content through the Blender 1, Blender 2, and tableting process (blending in the force feeder). Using the RTD model prepared by the method shown in 4.2., it is possible to predict how the variation caused by the LIW feeder propagates in the process and how it affects the quality of the final drug product, and to set the acceptable range of variation of the LIW feeder. Fig. 4 shows an image of predicting how the variation in feed rate due to disturbance in the LIW feeder would be transmitted to Blender 1, Blender 2, and the tablet press from the magnitude and duration of variation by the RTD model.

For example, a purple color pattern in Fig. 4 indicates a considerable variation in size but a short variation in duration. On the contrary, a pattern shown by blue indicates a small variation in size but a long variation in duration. If this kind of variation occurs in the LIW feeder, it takes \( \theta_2 \) for the PFR model to propagate the variation to Blender 1, and then the time-series change in the concentration in the blender is calculated with the CSTR model. In Blender 2, the PFR model is further delayed by \( \theta_3 \) to propagate the variation, and the CSTR model is used to calculate the time-series change in concentration. It was found that the magnitude became smaller and the duration of variation became longer after each of Blender 1 and Blender 2 than the variation caused by the LIW feeder. The RTD can express how the variation in the LIW feeder affects the CQA of Assay of the tablet finally after blending in the force feeder.

Therefore, using the RTD model, the magnitude and length of acceptable variation of LIW feeder can be established from its impact on the CQA of Assay and can be incorporated into the control strategy of the continuous direct compression.
Fig. 2 – RTD model and its characteristics.

| PFR Plug flow reactor | CSTR Continuous stirred tank reactor | Conversion model |
|-----------------------|--------------------------------------|-----------------|
| Characteristic        | Complete stirring tank                | Combined PFR and CSTR |
| RTD form              |                                      |                  |
| $\theta$              |                                      |                  |
| Time                  |                                      |                  |
| $\tau_1$              |                                      |                  |
| RTD Equation          |                                      |                  |
| $C_{in}(t - \theta) = C(t)$ | $C_{in}(t) = C(t) + \tau_1 \frac{dC(t)}{dt}$ | $C_{in}(t - \theta) = C(t) + \tau_1 \frac{dC(t)}{dt}$ (if $N = 1$) |

Table 5 – Example of the experimental method for the RTD parameter estimation and concentration change pattern obtained.

| Experimental method for RTD parameter estimation |
|-----------------------------------------------|
| **Impulse response**                          |
| Add tracers from the designated place during operation to monitor the changes in concentration. It has the advantages that the preparation can be performed with relatively small amounts of raw materials. |
| **Step Response**                             |
| Operate with a recipe in which the component concentration is changed at a certain time point to follow the concentration change until the component concentration reaches the set value. Since manual operations such as addition of tracer are not performed, there is less risk of varying (disturbing) the process and exposure to the operator (particularly high active compound) compared with the impulse response. |
| **Multistep Response**                        |
| Repeat the step response to follow the variable concentration. Long-term operation results in less variable data, but the amount of raw material required to generate the data is large. |

Concentration change pattern

As shown on the left of Fig. 5, even if a large transient change (blue line) occurs in the LIW feeder, if the API concentration in a tablet calculated by the RTD model is within the acceptance value/range (Fig. 5, green line on the left), it can be judged to be conforming, and the control such as diversion from the system can be performed by the RTD model only when the calculated API concentration exceeds the acceptance value/range as shown in the part enclosed by the purple dotted line on the right of Fig. 5.

Fig. 6 shows the acceptable range of variation of the LIW feeder calculated by the RTD model based on the above concept. Theoretically, the blue area in the figure is within the specification, and therefore the product can be judged as a conforming product. On the other hand, in normal
In commercial production, it is common to set Alert Limit (Action Limit) inside the upper and lower limits of the acceptable range, and it is appropriate to control it inside the boundary between In spec and Out of spec in Fig. 6. In addition, as shown in "3. Items to be controlled and managed in the process in continuous direct compression," if the degree of variation is substantial, it is considered that the control is performed depending on the situation such as stopping the machine.

4.4. **Notes on the control of continuous direct compression process using the RTD model**

As mentioned above, the RTD model can be a useful tool for controlling the continuous direct compression process. On the other hand, the points to consider when using this RTD model were summarized as follows.

[**Development of the RTD model**]
- The RTD model needs to be validated with actual experimental data.
- The RTD model may differ depending on the formulation of the product, machine, and manufacturing conditions; therefore, it is necessary to confirm the presence or absence of impact on the RTD model when they are changed.
- Since the RTD model is affected by the throughput of the process (kg/h), it is important to confirm in advance the upper and lower limits of the throughput within which the RTD model can be used.
The monitoring and control of the homogeneity of powder blend, which was out of scope of this study, is important in the actual manufacturing to assure the final drug product quality in the continuous direct compression process.

5. Conclusion

We presented a control strategy for continuous direct compression processes, as an outcome an industry-academia-regulatory authority research project in Japan. After discussions in the expert group, the component ratio and blended powder content were selected as the items requiring the control method specific to the continuous manufacturing different from the batch manufacturing. The control and management of the LIW feeder for each component were deemed the most important, and the RTD model was regarded effective for setting the control range and controlling the LIW feeder. Based on these ideas, the concept of process control using RTD model was summarized. The presented contents can serve as a solid fundament for adopting a new control method of continuous direct compression in and beyond the Japanese market. The content presented in this article is an example, and it should be noted that the use of RTD models varies depending on the product and process characteristics to be applied or the purpose of application, including how to control the manufacturing process, how to validate the RTD model and how often the RTD model should be verified.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article. The views expressed in this manuscript by the authors are personal and do not necessarily reflect the official views of the Pharmaceuticals and Medical Devices Agency (PMDA).

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