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Material tracking in a continuous direct capsule-filling process via residence time distribution measurements

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ABSTRACT

Continuous production of pharmaceuticals requires traceability from the raw material to the final dosage form. With that regard, understanding the residence time distribution (RTD) of the whole process and its unit operations is crucial. This work describes a structured approach to characterizing and modelling of RTDs in a continuous blender and a tamping pin capsule filling machine, including insights into data processing. The parametrized RTD models were interconnected to model a continuous direct capsule-filling process, showing the batch transition as well as the propagation of a 2 min feed disturbance throughout the process. Various control strategies were investigated *in-silico*, aiding in the selection of optimal material diversion point to minimize the material waste. Additionally, the RTD models can facilitate process design and optimization. In this work, adaptions to the capsule filling machine were made and their influence on the RTD was examined to achieve an optimal machine setup.

1. Introduction

Continuous manufacturing (CM) is becoming increasingly important in the pharmaceutical industry. The transition from batch to continuous processing is driven by a shorter time to market of assets (both development and process transfer) due to the absence of scale-up, which is one of the main advantages of CM. Lab-scale equipment or small-scale industrial equipment can be used in industrial production since the amount of final product is determined by the production time. Moreover, smaller equipment reduces the footprint of the plant (Rantanen and Khinast, 2015; Ierapetritou et al., 2016). Sophisticated supply chain management can help to decrease in the storage capacity (Srai et al., 2014). Increasing agility in manufacturing by effectively increasing flexibility of the supply chain is another major advantage.

The regulatory authority in the USA (FDA) endorsed continuous pharmaceutical manufacturing starting in 2004 with the analytical technology (PAT) initiative (FDA, 2004 19). Ever since, new and revised guidelines introducing CM into the pharmaceutical industry have been published.

In terms of quality control for CM, traceability of material (material tracking) throughout the process is a key consideration (Engisch and Muzzio, 2016). Thus, the objective of this work was to achieve process understanding with regard to the residence time distribution (RTD) in capsule fillers. The basis for RTD modeling is given in various texts, and done typically via axial dispersion models or by a cascaded CSTR (tanks-in-series) model (Engisch and Muzzio, 2016; Martinetz et al., 2018; Kruisz et al., 2017; Wagner et al., 2018a,b; Rehrl et al., 2016; Chen, 2004). This work focuses on RTD model development based on CSTR models. The CSTRs are represented in the form of transfer functions, which allows to apply standard control methods when using such models for model-based controller design (Sugar Spheres, 2018). Those RTD models in Laplacian domain have been presented previously by Martinetz et al. (2018) and Kruisz et al. (2017) for dry granulation processes. Furthermore, the developed RTD models enable *in-silico* material tracking with the specific focus on capsule filling. Such process knowledge can facilitate batch definition by predicting transition regions between two raw material batches (Fig. 1). The influence of process parameters on the filling performance, e.g., fill weight and fill weight variations were investigated by Wagner et al. (2018a,b).

Material tracking concerns traceability of disturbances introduced into the process mainly by feeders (Engisch and Muzzio, 2016), as well as the effects of feeder failures on the intermediate (blend) and final product. RTD models can be used to simulate raw-material batch changes and various process disruptions, such as hopper refilling. Furthermore, the models can be used to identify the time periods at which the API concentration is out-of-spec (OOS). Thus, the models are a valuable tool for calculating the required amount of rejected OOS material. Usually, the concentration of an API is critical, which in this

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Nomenclature

E	exit-age-distribution
$P(s)$	transfer function
t_x	time until cumulative tracer concentration/intensity reaches x%.
W	wash-out function
σ^2_{exp}	variance of exit-age-distribution
σ_{exp}	standard deviation of exit-age-distribution
τ	mean residence time

Abbreviations

CM	continuous manufacturing
cph	capsules per hour
CQA	critical quality attribute
CSTR	continuously stirred tank reactor
LIF	light induced fluorescence
PBH	powder bed height
PFR	plug flow reactor
PSD	particle size distribution
QTPP	quality target product profile
RTD	residence time distribution
tpm	tamps per min in 1/min

Subscripts

bl	blender
cf	capsule filler
CSTR	continuous stirred tank reactor
exp	experimental
plant	plant (direct capsule filling line)

work is substituted by the tracer concentration. The paper at hand introduces a control concept for the API concentration as a main critical quality attribute (CQA) after blending and dosing into capsules which can be integrated into model predictive control (MPC) similar to Rehrl et al. (2016). Selected disruption events were simulated for two throughput rates and two possible discharge points were compared in terms of estimated amount of waste material.

An important parameter of all unit operations is the mean residence time (MRT) τ during which the material resides in the unit, which can be calculated as

$$\tau = \frac{V}{\dot{V}} \tag{1}$$

Clearly, for a constant density

$$\tau = \frac{m}{\dot{m}} \tag{2}$$

Here, V is the hold-up volume, $\dot{V}$ is the volumetric flow rate, m is the mass and $\dot{m}$ is the mass flow rate. For the same throughput a smaller amount of material (lower hold-up) in the process leads a shorter mean residence time. A low value of τ indicates a reduction in the waste material during start-up and shut-down of the processing line. The RTD can be interpreted as the system's impulse response (Chen, 2004). A narrow and short RTD leads to sharp batch transitions and shorter discharge times compared to a system with significant back-mixing. Although a long MRT and a broad RTD can facilitate mixing and can dampen disturbances, it results in long batch transition times (see red boxes in Fig. 1). The desired system dynamics, i.e., MRT and width of the RTD, have to be selected considering the actual process and disturbances. In this work, the benefits and drawbacks of broad and narrow RTDs are compared.

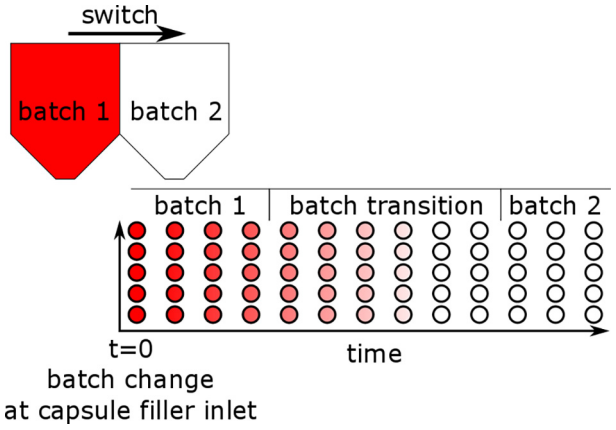


Fig. 1. Batch definition: transition between raw material batches.

The goal of this work is the development of a RTD model for a direct capsule filling line, from which the batch transition time and material concentrations along the process can be calculated. To get an impression of the influence of process settings, the RTD of capsule filler was determined for three inserts (see Table 1) and for two throughputs. Regarding the blending step, the influence of the blender's rotational speed on its RTD was investigated at three throughput levels matching those in the capsule-filling process.

This paper is structured as follows: the Material and Methods section describes the bulk powder material, the coloring procedure for RTD measurement and the experimental setup in the blending and capsule-filling experiments. Furthermore, details on the data processing and the developed RTD models are provided, as well as the control concept with two possible discharge points. The Results and Discussion section focuses on the comparison of the three inserts. Lastly, the conclusion highlights the significant results and further applications.

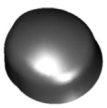
2. Materials and methods

The following section describes the materials used and methods applied to determine the RTD of the continuous capsule-filling process (Fig. 2). The section is structured as follows. First, the processed materials are described, followed by the process line description, starting with the main component, the capsule filling machine, as well as blender and the feeders. The section continues with a detailed description of the experimental procedures as well as the data acquisition method and data processing to determine the RTD of the blender and the capsule filling machine. The last part in this section deals with the derivation of RTD models for blender and capsule filling machine.

2.1. Material

All experiments were conducted with sugar pellets (Pharm-a-Spheres®, Hanns G. Werner GmbH + Co.KG, Tornesch, Germany),

Table 1
Overview of the inserts used in the RTD experiments. The bowl volume is the free volume of the bowl filled with powder to reach the desired powder bed height (PBH) of 20 mm.

Tag	Reference	Geometry 1	Geometry 2
Shape			
Bowl volume – 20 mm PBH	283 cm^3	361 cm^3	265 cm^3