International Journal of Pharmaceutics 528 (2017) 334–344

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

RTD modeling of a continuous dry granulation process for process control and materials diversion

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ARTICLE INFO

Article history:
Received 3 April 2017
Received in revised form 31 May 2017
Accepted 1 June 2017
Available online 3 June 2017

Keywords:
Continuous manufacturing
RTD modelling
Out-of-spec handling
Dry granulation
Process control

ABSTRACT

Disturbance propagation during continuous manufacturing processes can be predicted by evaluating the residence time distribution (RTD) of the specific unit operations. In this work, a dry granulation process was modelled and four scenarios of feeding events were simulated. We performed characterization of the feeders and developed RTD models for the blender and the roller compactor based on impulse-response measurements via color tracers. Out-of-specification material was defined based on the active pharmaceutical ingredient (API) concentration. We calculated the amount of waste material at various diversion points, considering four feeder-related process-upset scenarios and formulated considerations for the development of a control concept. The developed RTD models allow material tracking of materials that may be used for following the spread contaminants within the process and for batch definition. The results show that RTD modeling is a valuable tool for process development and design, as well as for process monitoring and material tracking.

1. Introduction

In the pharmaceutical industry, a transition from batch processing to continuous manufacturing (CM) is taking place (Plumb, 2005; Lee et al., 2015) due to the advantages of CM, such as smaller production equipment, higher flexibility and elimination of scale-up issues. By applying CM, the amount of product is determined by the production time rather than by equipment size. Thus, the same equipment can be used for development and industrial production (Srai et al., 2015). Furthermore, through CM the amount of material in stock can be reduced via supply chain management. In addition, CM approaches are more flexible and agile and speed up the development process (e.g., during the transition from small-scale clinical trials to industrial-scale batches). This reduces time-to-market and provides extended patent life time (Schaber et al., 2011).

Process understanding is a critical prerequisite for CM. To facilitate process understanding, the Food and Drug Administration (FDA) launched guidelines for the development of Process Analytical Technologies (PAT) in 2004 (FDA, 2004). Moreover, the International Conference on Harmonization (ICH) guidelines (Q8 (International Conference on Harmonisation, Q8(R2), 2009) and Q10 (International Conference on Harmonisation Q10, 2008)) were released. These guidelines created a new mindset in terms of quality, incorporating process monitoring of the intermediates and not only of the end product.

For assuring a constant product quality within a CM framework, real-time process monitoring of intermediate quality attributes is a prerequisite. Handling out-of-spec (OOS) material is a significant challenge in this context. In general, production disturbances may lead to faulty intermediate products, resulting in an OOS end product. In batch processing, an entire batch must be destroyed due to OOS material, which can be costly since a whole batch is lost and the disposal can be expensive. In CM, it is possible to reject only the OOS material at some point during the process, as well as counteract process disturbances and keep the final product in-spec. Due to interconnection of all unit operations, reacting adequately requires deep process knowledge and a sophisticated control concept.

The decision whether to divert material (material diversion or segregation) can be based on monitoring the process parameters or in-line measurement of critical quality attributes (CQAs). In this work, a general concept of concentration measurements using NIR

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http://dx.doi.org/10.1016/j.ijpharm.2017.06.001
0378-5173/

Nomenclature

Abbreviations

RTD	Residence time distribution
API	Active pharmaceutical ingredient
CM	Continuous manufacturing
OOS	Out-of-Spec
FDA	Food and drug administration
ICH	International conference on harmonization
PAT	Process analytical technology
NIR	Near infrared spectroscopy
LIW	Loss-in-weight
CQA	Critical quality attribute
FBU	Feeding/Blending unit
RC	Roller compactor
EXC	Excipient
RSD	Relative standard deviation
RGB	Red-Green-Blue
LAB	Lightness, a color value, b color value

Variables

$\dot{m}$	Mass flow
σ	Standard deviation
$N(0,\sigma)$	Normal distribution with zero mean and σ as standard deviation
t	Time
C	Concentration
E	Residence time distribution
t_x	Time until x% tracer removed from the system
τ	Mean residence time
P	Transfer function
$\mathscr{L}$	Indicating Laplace transform
T	Time constants
k,K	Scaling constants
y	Measured concentration/intensity
$\hat{y}$	Predicted concentration
T_s	Sampling time
F_s	Sampling frequency
d_{50}	Mean particle size
f	Frequency
ω	Rotational speed

Subscripts

0	Nominal
bl	Blender
RC	Roller compactor
feeder	Feeder
API	Related to API
EXC	Related to EXC
in	Inlet
out	Outlet
i	Variable for iteration over samples
screw	Feeder screw

and other PAT tools is presented for a *continuous dry granulation line*. NIR is a commonly used technique to measure the API concentration. A model is applied which predicts the concentration based on calibration measurements. The prediction is not instantaneous since data acquisition (integration time) and solving the model require time, which has to be taken into account when developing diversion strategies. Hence, the diversion points have to be chosen such that the OOS material can be detected before the diversion points are reached. To determine if the locations of the measurement- and diversion-points are chosen in a suitable manner, the RTD of the process must be analyzed. Furthermore, with regard to regulatory approval of a continuously-manufactured pharmaceutical product, material tracking is crucial, i.e., for establishing a "bill of materials (BOM)". Knowing the RTD allows calculation of the position of material introduced into the process at any given time (Engisch and Muzzio, 2015). Process simulation is a valuable tool in this context (Boukouvala et al., 2012, 2013).

Dry granulation is an important unit operation in pharmaceutical manufacturing, making it possible to process poorly flowing and highly cohesive materials by enhancing their flowability via particle size enlargement (Reynolds et al., 2010; Bindhumadhavan et al., 2005). Moreover, segregation and dusting during subsequent processing steps can be decreased. Furthermore, this type of particle size enlargement requires no liquid addition, allowing to process moisture-sensitive or easily dissolving materials. In this work, a dry granulation step via roller compaction (RC) was combined with a feeding/blending unit (FBU) and a tablet press to create a continuous pharmaceutical process for tablet manufacturing (similarly to the dry granulation presented in (Simonaho et al., 2016)) shown in Fig. 1.

In the line considered, the tablet press is the last in a sequence of continuously operated units. It typically has a hopper, which may be used as buffer in case of diversion OOS material before it reaches the tablet press. Accurate diversion of OOS material can be achieved via PAT (e.g., near infrared spectroscopy) (Skibsted and Engelsen, 2017; Scheibelhofer et al., 2012; Wahl et al., 2014), better process understanding and sophisticated predictions of the concentrations based on the internal control/monitoring systems of the unit operations (e.g., loss-in-weight (LIW) feeder signal).

Our work focused on the development of a concept for OOS detection based on deviations in concentrations. The proposed models, presented in Section 2.1, Sections 2.2 and 2.3 provide an experimental description and highlight the data-processing approach. Simulations of disturbance scenarios are discussed in Section 2.4, with a comparison of diversion times and waste material. Finally, simulations are presented for a continuous dry granulation line, with the evaluation of various measurement- and diversion point-combinations and prediction of the amount of waste material in Section 3. Specifically, material diversion after the blender and the RC unit was considered and the impact of process disruptions by the feeder on the amount of OOS material was studied.

2. Materials and methods

2.1. Model development

Based on the RTD of each unit operation, concentrations after each processing step can be predicted and used for the development of a control concept. Moreover, studies of different material diversion scenarios can be carried out and hopper design (i.e., optimized storage capacity) can be based on rational science. In this work, we focused on the material diversion strategies in combination with PAT measurement positions to address fluctuations of the API concentrations.

The feeder model was developed under the assumption that the feeder has a constant feed rate with some additional noise and a periodic disturbance caused by the feed screw. A start-up phase with higher mass-flow deviations due to internal signal processing/calibrations of the feeder was not considered. The mass flow rate of the feeders is given by Eq. (1), where $\dot{m}_0$ is the nominal mass flow rate (set-point), ω_{feeder} is the screw speed in revolutions per