FLOWSHEET MODELING OF A CONTINUOUS DIRECT COMPRESSION TABLETING PROCESS AT PRODUCTION SCALE

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Abstract

A flowsheet model for a continuous direct compression tableting process is developed and applied to process data. The model contains powder feeding, blending and tablet compaction unit operations. The dataset was provided by Merck & Co., Inc., Kenilworth, NJ USA using a GEA ConsiGma™ continuous direct compression process designed for a 50 kg/h throughput using a six ingredient, potentially commercial, formulation. A tanks-in-series methodology is used to model the transport of powder through the blending units and the tablet press model allows upstream changes in composition to be propagated to the tablet properties. The flowsheet model performed well based on the available dataset and will be used for further process optimization as the process approaches commercial production.

Keywords

Flowsheet modeling, pharmaceutical manufacturing, powder blending, tablet compaction, sensitivity analysis.

Introduction

Pharmaceutical manufacturing is traditionally carried out using batch processes, which are less efficient and more expensive than continuous processes (Leuenberger and Betz, 2007). Both regulators and industry are beginning to embrace continuous manufacturing along with its significant advantages in process development, product quality and cost (Plumb, 2005). Flowsheet modeling is a key enabling technology for this transition and integrates well with the FDA's quality by design approach (ICH Expert Working Group, 2009). A flowsheet model for a continuous direct compression (CDC) tableting process is developed here and is tested against data obtained at production scale.

In process modeling, a flowsheet model contains descriptions of all unit operations in a given process to approximate the whole plant/process operation. A key strength of this type of model is that the effect of upstream disturbances on downstream unit operations can be investigated. Furthermore, control strategies that use measurements of one unit operation to manipulate a variable in a different unit operations can be explored (Boukouvala et al., 2012).

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The CDC process used in this work was the GEA Pharma Systems ConsiGma™ CDC-50. This unit consists of up to six loss-in-weight (LIW) screw feeders, two continuous blenders, an NIR probe for blend composition measurements and a tablet press. In this work a six-ingredient formulation was used and the CDC was configured so that the API and three excipients were fed to the first blender (using one feeder per ingredient) and two lubricants were introduced to the second blender along with the powder from the first blender. The NIR probe is placed so that measurements of composition are taken as powder leaves the second blender and enters the tablet press. A block flow diagram of the CDC process used in this work can be found in Figure 1.

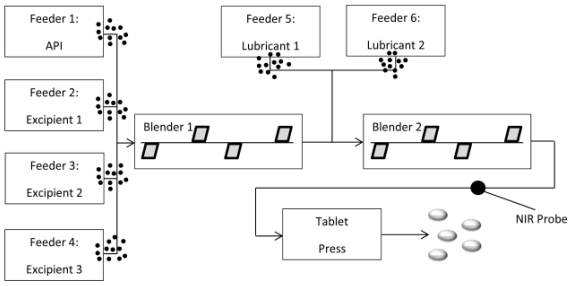

Figure 1. Block flow diagram of the GEA ConsiGma™ CDC-50 process used in this work.

The CDC unit was run at production scale, meaning the models developed are already at-scale and therefore do not require further work to be used in commercial applications.

Modeling Methodology

The CDC flowsheet model used in this work was implemented in the gSOLIDS[1] modeling environment which contains a number of unit operation library models and allows for the addition of custom equations and models for specific processes.

Powder Feeding

The first units in the flowsheet model are the LIW feeders. In this work, the feeders are assumed to be ideal. That is, the mass flowrate of each feeder is kept constant at its set-point and is not affected by hopper fill level or screw speed.

Powder Blending

The two continuous blending units in the CDC process are modeled using a tanks-in-series approach to capture the residence time distribution (RTD). Blend uniformity is neglected here seeing that for all operating conditions used to generate the dataset the relative standard deviation of the API concentration was less than 5%, which is considered to be homogenous in the pharmaceutical industry (Esbensen et al., 2016). Other flowsheet modeling efforts for CDC have utilized population balance models seeing as they describe both RTD and blend uniformity (Singh et al., 2015). The tanks-in-series approach was chosen because it fits well within a flowsheet model and does not require discrete element method simulations needed to parameterize the blending population balance model (Rogers et al., 2014).

Each blending unit is represented by one plug flow reactor (PFR) and two continuously stirred tank reactors (CSTR). This configuration was chosen so that the number of tanks in the flowsheet model is fixed. This allows the same flowsheet to be used for all experimental conditions, with changes to reactor volume and length, and not number, reflecting changes in operating conditions.

There are three mixing units used in the flowsheet model: 1) Blender 1, 2) Blender 2 and 3) Feed frame for the tablet press. While the feed frame of the tablet press is not intended for powder blending there is some mixing that occurs there and its residence time should be captured in the model.

The PFRs and CSTRs in the flowsheet model are represented by the gSOLIDS "belt conveyor" and "mixing tank" library models respectively. Seeing that the number of tanks is fixed, the model parameters required to define the process are the belt dimensions (length and width), belt velocities and tank volumes. The belt width and velocity are held constant in all simulations so that the only two model parameters that can affect the RTD are the belt length and tank volume. The choice of fixing the belt velocity and changing the belt length was made arbitrarily.

Parameter estimation is used to find the model parameters with the experimental RTD curves generated from impulse tests. The well-known reactor engineering equation for the exit age distribution during an impulse in a CSTR-in-series is used for the parameter estimation (Levenspiel, 1999). The mean residence time is used to calculate the tank volumes in the flowsheet model and a lag time component is added which is used to determine the belt length, see Eq. 1.

$$\tau E(t) = \begin{cases} 0, t \le t_{lag} \\ \left(\frac{t - t_{lag}}{\tau}\right)^{N-1} \frac{N^N}{(N-1)!} \exp\left(\frac{-(t - t_{lag})N}{\tau}\right), t > t_{lag} \end{cases} \quad (1)$$

[1]Process Systems Enterprise, London, UK; www.psenterprise.com

Where τ is the mean residence time (s), t_{lag} is the lag time (s) and N is the number of tanks (unitless).

As mentioned previously, the number of tanks is fixed in the flowsheet model and therefore fixed during the parameter estimation. However, the value for number of tanks used in the estimation depends on where the impulse was introduced and where its effect was detected. Table 1 summarizes the various combinations possible in the CDC model here, i.e., where impulses can be introduced and where they can be detected in the real system. The subscript *B1* denotes blender 1, *B2* denotes blender 2 and *FF* denotes the tablet press feed frame.

Table 1. Summary of number of tanks used in parameter estimation depending on where the impulse was added and detected.

Impulse added	Impulse detected	Number of tanks	Mean residence time
Blender 1 entrance	Tablet press exit	6	$\tau_{B1}+\tau_{B2}+\tau_{FF}$
Blender 1 entrance	Blender 2 exit	4	$\tau_{B1}+\tau_{B2}$
Blender 2 entrance	Tablet press exit	4	$\tau_{B2}+\tau_{FF}$
Blender 2 entrance	Blender 2 exit	2	τ_{B2}

Using different impulse tests and the relationship between the mean residence time of the various blending units, an individual mean residence time for each blending unit can be obtained and used to determine the reactor volumes in the flowsheet model.

Tablet Press

The tablet press model used in the CDC flowsheet model is taken from the gSOLIDS library with some custom equations added. Custom relative density equations that included the initial relative density were incorporated (see Table 2) so that upstream disturbances could be captured in the tablet press. It should be noted that tablet relative density is defined as the ratio of the tablet bulk density and the tablet skeletal density.

The nomenclature used in Table 2 is; P is the applied pressure (MPa), D_0 and D are the initial relative density and relative density after compaction respectively (unitless), A_i and B_i are constants that are determined from experimental data by parameter estimation in gSOLIDS.

Table 2. Relative density equations added to the tablet press model.

Equation name	Equation	Reference
Kawakita	$\frac{D}{D-D_0}=\frac{A_1}{P}+B_1$	Mazel et al., (2011)
Cooper and Eaton	$\frac{D-D_0}{1-D_0}=B_2\exp\left(\frac{-A_2}{P}\right)+\left(\frac{-A_3}{P}\right)$	Sivasankaran et al., (2011)
Van Der Zwan and Siskens	$\frac{D-D_0}{1-D_0}=B_4\exp\left(\frac{-A_4}{P}\right)$	Sivasankaran et al., (2011)

The tablet hardness, H (N), is calculated from the relative density using a theoretical model shown in Eq. 2 (Kuentz and Leuenberger, 2000).

$$\ln\left(1-\frac{H}{H_{\max}}\right)=D-D_c+\ln\left(\frac{1-D}{1-D_c}\right) \quad (2)$$

Where H_{max} is the maximal tablet hardness at zero porosity (N) and D_c represents the critical relative density (unitless) which is the lowest relative density that can occur during the tablet compaction process. These two parameters are constants that are determined from experimental data by parameter estimation.

Experimental Methodology

The modeling approach was tested against a dataset collected by Merck & Co., Inc., Kenilworth, NJ USA. Because of the proprietary nature of the product formulation, the names and compositions of the particular components cannot be given. However, the conclusions drawn from using this dataset to test the modeling approach remain valid and can be applied to other formulations.

Blending experiments

A three level design of experiment (DOE) was used to generate the experimental dataset and three process parameters where investigated: 1) throughput, 2) blender 1 impellor speed and 3) blender 2 impellor speed. The values used for these operating parameters are given in Table 3.

The API composition in the blended powder was determined by inline NIR (near infra-red) spectroscopy which was calibrated by HPLC (high-performance liquid chromatography). The API weight percentage is reported as a normalized value to blind the real concentration. As mentioned previously, the RTD was measured by performing impulse tests. A known amount of the API was added at the entrance of blender 1 or blender 2 at a known time and the changes to the composition resulting from the impulse were detected by the NIR probe.

Table 3.Operating parameter values used in the DOE to generated the powder blending dataset.

DOE point	Throughput (kg/h)	Blender 1 speed (rpm)	Blender 2 speed (rpm)
Low (L)	25	180	120
Middle (M)	50	315	210
High (H)	90	450	300

The RTD can then be calculated from the NIR data using Eq. 3. It should be noted that the NIR probe records a spectrum of the powder once a second, so that a concentration can also be calculated once a second.

$$E(t) = \frac{C(t)}{\int_0^\infty C(t).dt} \tag{3}$$

For some of the DOEs there was also rapid tablet sampling following the API impulse. The API concentration of those tablets was measured with NIR. This allows the RTD to be tracked through the tablet press as well as the two blending units as described in Table 1.

Tablet compression experiments

Tablets of 400 mg were produced using the CDC tablet press. Tablet samples were taken every 15 minutes and 10 individual tablets were measured for weight, thickness and hardness using a Dr. Schleuniger manual tablet tester. The tablets were compressed within a range of 6.7 to 34.4 kN. The tablet bulk density was calculated by dividing the measured tablet weight by the tablet volume as calculated from its dimensions. It can be seen in Table 2 that the relative density equations are written in terms of pressure so the measured compaction force was converted into a pressure.

Results and Discussion

Blender RTD

The tanks-in-series blender models are meant to describe the RTD of the blending units in the CDC. Parameter estimation was performed to determine the mean residence time and lag time associated with each blending unit from the experimental impulse tests. This information was used to determine belt conveyor lengths and mixing tank volumes used in the flowsheet model. These results of a parameter estimation using the *E(t)* distribution form the M-M-M experimental condition are show in in Figure 2.

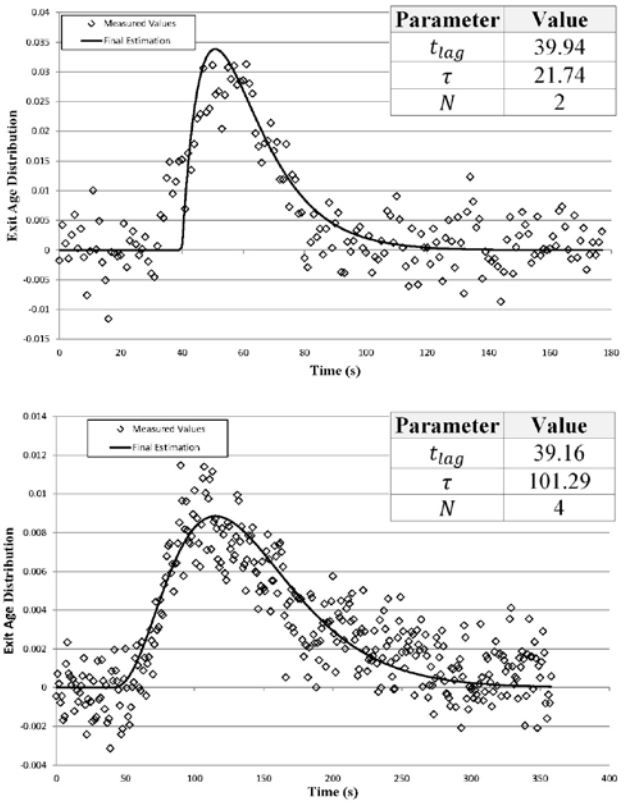

Figure 2. Typical parameter estimation results (using the M-M-M experimental data) showing an impulse added to blender 2 (top) and an impulse added to blender 1 (bottom). The values for the lag time and mean residence time from the parameter estimation are inset.

The results from the parameter estimation using data from all impulse tests were then used to construct flowsheet models using the modeling methodology discussed previously. The performance of the flowsheet models to describe the RTD in the blending units can then be tested by simulating the impulse tests. The impulse test in the real system is simulated in the flowsheet model by increasing the mass flowrate of API for one second of simulation time by an amount that is equal to the impulse used in the experiment, e.g. an increase in the API mass flowrate of 100 g/s for a period of one second will introduce an extra 100 g of API. The composition of the API in the powder exiting blender 2 can then be compared to the raw API concentration as determined by NIR. Figure 3 shows the results of the impulse test simulation.

It can be seen in Figure 3 that the tanks-in-series approach used in the flowsheet model is able to describe the RTD of the CDC blending units for the operating conditions used to generated the dataset.

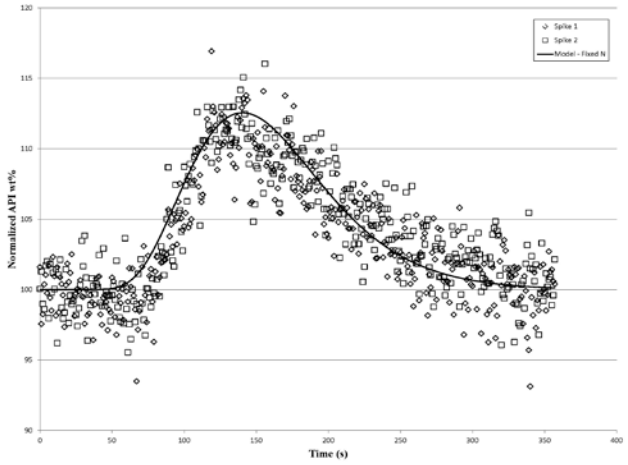

Figure 3. Simulated impulse test for the CDC blending units in the flowsheet model constructed for the H-M-M experimental data.

Tablet Press

The parameter estimation in all the relative density equations in Table 2 and the hardness equation (Eq. 2) is performed in gSOLIDS. The relative density and hardness determined with those equations are compared to the experimental measurements in Figure 4 with the values of the estimated parameters inset. All equations are able to describe relative density and hardness within the compaction force range used to generate the experimental dataset.

CDC Flowsheet Model

The results presented so far have focused on the blending and tablet press unit operations, i.e. demonstrating that the tanks-in-series blending model can predict RTDs and the tablet press model can predict relative density and hardness for the experimental dataset gathered to date. However, the purpose of the flowsheet model is to investigate how disturbances upstream affect downstream processes. In order to demonstrate this, the impact the impulse tests, used to demonstrate the blending models, have on the tablet press are shown. Figure 5 shows the impact that the impulse test has on the composition of the tables produced in the tablet press. It is clearly seen that the impulse is captured in the API concentration of the tablets as measured by NIR and the model can reasonably predict this.

Changes in the blended powder bulk density due to the impulse should also affect the relative density and therefore hardness of the tablets produced. This is demonstrated in Figure 6, which shows the tablet hardness during an impulse test when the Kawakita relative density equation is used in the tablet press model. It should be noted that this is purely a simulation result as hardness measurements were not performed on the tablet samples taken during an impulse test. Furthermore, this result can only be achieved if the equation chosen to calculate relative density considers the initial relative density. Other equations for tablet relative density that only consider the compaction force/pressure and not the initial, or pre-compaction, relative density would not be able to produce the result seen in Figure 6.

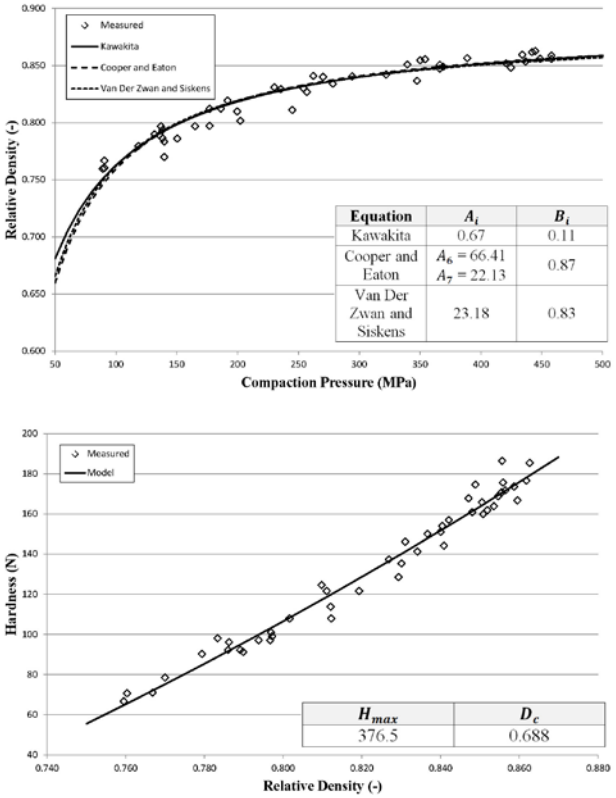

Figure 4. Comparison of model results with experimental measurements for relative density (top) and hardness (bottom) with the estimated parameters inset.

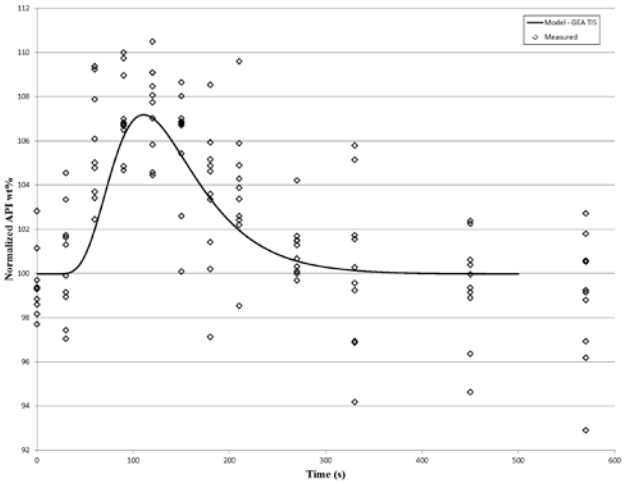

Figure 5. Impact of the impulse test on the composition of tablets exiting the tablet press.

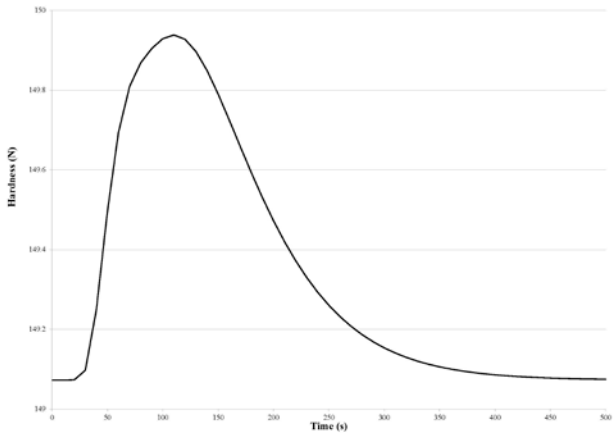

Figure 6. Impact of the impulse test on the hardness of tablets exiting the tablet press.

Conclusions

A flowsheet model for a continuous direct compression tableting process is developed using a tanks-in-series methodology and a number of tablet relative density equations. The parameter estimation methods used to determine the flowsheet model parameters are described and the performance of the model is demonstrated for the residence time distribution and tablet hardness by comparing model calculated values to measurements taken from the process operating at production scale. The model was found to perform well with the collected dataset. The functionality of the flowsheet model is also demonstrated by showing how a disturbance in API feeder, simulating an impulse test, propagates through the blenders to the tablet composition and hardness. The performance of the flowsheet model is promising and indicates that it can be used applications such as sensitivity analyses, control strategy investigation and design space exploration.

Acknowledgments

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