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Research paper

Analysing drying unit performance in a continuous pharmaceutical manufacturing line by means of mass – Energy balances

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ABSTRACT

The current trend in the pharmaceutical industry to move from batch-wise to continuous production processes strengthens the need for monitoring and controlling the process in-line. The ConsiGma™ continuous tableting line collects data of the different subunits in real-time, but these are not really used. In this paper the data of the six-segmented fluidized bed dryer in the line are used for the development and evaluation of a mass and energy balance. The objectives are multiple: (1) prediction of the moisture content of the granules leaving the dryer solely based on the currently logged data and (2) prediction of the gas outlet temperature to check the mass balances. Once a validated system is established the gas temperature in different horizontal sections of the drying unit can be predicted. Calculations are also used to identify errors in the system and to propose alternative sensor locations. A calibration is performed in order to predict the evaporation rate. The balances were able to predict both the moisture content of the granules at the end of the drying process and the gas outlet temperature quite accurately. Combining the gathered information with the height of the bed in the fluidized bed can be used to predict the gas temperature in different horizontal sections of the dryer. An extra sensor measuring the gas temperature and the humidity at the wet transfer line would increase the accuracy of the calculations. An extra gas velocity sensor at the outlet would be useful to incorporate an extra supervision of the calculations.

1. Introduction

1.1. State of the art process monitoring and controlling in pharmaceutical industry

One recent trend in pharmaceutical manufacturing is the shift from batch-wise to continuous production processes, not only in the synthesis of small molecules [1,2], but also in formulation [3,4]. The traditionally applied batch processes mostly rely on off-line post-process time-consuming and less efficient laboratory testing to evaluate the quality of the product [5]. Continuous production processes, relying on in-line measurements and real-time adjustment of sensitive process variables would be a major step forward towards more efficient production routines. A batch is well defined, and as such it is easy to perform a quality assurance, since a batch can simply be accepted or rejected based on a quality assessment. But since quality is only checked after the process in traditional manufacturing, it is impossible to control the process on the basis of such measurements. A bad batch is simply lost. However, monitoring the process during operation allows interfering during production (i.e. process control) which is more economical as the loss in off-spec product is limited [5,1,6]. A general problem within the pharmaceutical industry is the strict regulations. Once a process is approved by the regulatory authorities, it is generally accepted that it is almost impossible to change something in the way of processing without re-documentation and re-approval [1,5]. The Food and Drug Administration (FDA) intended to promote innovation by publication of the Process Analytical Technology (PAT) guidance. An important concept is Quality By Design (QbD), defined as 'a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management' [7].

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The equipment to produce tablets in a continuous mode is limited up to now. The ConsiGma™ continuous tableting line (Collette™, GEA Pharma Systems, Wommelgem, Belgium) enables the production of tablets from powders in 20 min. It consists of the ConsiGma™ high shear granulator and fluidized bed dryer, combined with the GEA Courtoy MODUL P rotary tablet press [8]. Lödige Process Technology has the CWG line which is a continuous wet granulation line and is also a complete system from raw material dosing till tabletting [9,5]. In this work, the focus is on the continuous fluidized bed drying system of the ConsiGma™ continuous tabletting line. Real-time on-line measurements are continuously logged. The logged data will be processed using a mass and energy balance in order to monitor the process in real time.

Several in-line measurement tools are available for the monitoring and control of pharmaceutical manufacturing processes. In-line measurements provide real-time data about a process, and can thus be used as inputs to control the process operation. Process analysers can be divided into the univariate (such as temperature, pressure, and gas velocity) and multivariate process measurements, which provide biological, physical, chemical, etc. characteristics of the material. The determination of the moisture content of material during processing of solids can be achieved using several techniques. However, a lot of techniques that are currently available are not appropriate for use under harsh process conditions. Time domain reflectometry and transmissometry, capacitance probes, electrical resistance measurements, microwave spectrometry are all sensitive to the bulk density of the monitored system [10]. Other techniques are not able to measure the moisture content accurately due to the presence of hydrogen atoms in any other substance than water. This is the case for Nuclear Magnetic Resonance (NMR) or neutron absorption. Besides moisture content, Near Infra-red Spectroscopy (NIRS) is also able to provide information related to particle size. An advantage of the technique is its non-destructive nature. Moreover, Near Infra-red Spectroscopy (NIRS) is available against a reasonable cost, is fast, and is relatively immune to changes in bulk density caused by granule growth [11,12]. Frake et al. described Near Infra-red Spectroscopy (NIRS) as an in-line tool to obtain the granule moisture content and particle size of a fluidized bed granulation process. It allows modification of process conditions during operation as well as end-point identification [11]. However, attention should be paid to prevent the formation of solid deposits on the probe [10]. Chablani et al. used Near Infra-red Spectroscopy (NIRS) to measure the granules' moisture content produced using the ConsiGma™. The application of Near Infra-red Spectroscopy (NIRS) as a Process Analytical Technology (PAT) tool during continuous manufacturing is promising [13]. Besides Near Infra-red Spectroscopy (NIRS) spectroscopy, several other Process Analytical Technology (PAT) tools have been examined for moisture content assessment during processing of pharmaceutical solids. Porthoghese et al. described the use of triboelectric probes to measure solid moisture content during fluidization. Being inexpensive, very sensitive probes without requiring any maintenance makes them attractive [10]. Microwave Resonance Technology (MRT) has been implemented in fluidized bed dryers and provides precise and accurate results for the granule moisture content independent of product density [14]. The technique was validated using reference methods (Loss On Drying (LOD)/Infra-red light) and Karl Fisher titration. Wang et al. used Electrical Capacitance Tomography (ECT) for the on-line measurement of the solid moisture content in a batch fluidized bed dryer. The measured value can be used for implementation of a closed-loop control strategy [15]. Including in-line monitoring obviously requires extra probes and software for data processing, and as such extra costs. In some cases the pharmaceutical production equipment already has sensors in place, without using them for specific monitoring or control tasks. Hence, with no extra cost these data can potentially be sufficient for monitoring and controlling the process, hereby guaranteeing product quality.

1.2. Error propagation of measured model input variables into model output variables

Any measured variable is prone to measurement errors and contains an inherent uncertainty. This will have an impact when using these measurements in further calculations (e.g. mass balance checks, computing control actions, etc.). An error propagation enables the operator to quantify the cumulative effect of errors in the input data. Another option would be the use of more accurate sensors to minimise the error on calculated output. Moreover, the quest for more accurate sensors results often in more expensive sensors, which is of course important in a production process.

In control applications, one can use data reconciliation techniques in order to reduce the impact of erroneous data [16], whereas uncertainty propagation can be used for calculations based on the raw data. Error propagation is a methodological tool to quantify the uncertainty on a model output, given the source of uncertainty and its specifications (e.g. variance) are known. Typically this is done by construction of output uncertainty boundaries. The uncertainty on parameters and variables is hereby propagated to the output. Different methods are available depending on the model (non-)linearity. Simple linear models can use classical error propagation techniques. More complex models can make use of linear error propagation or differential analysis. Uncorrelated inputs for the uncertainty propagation have an advantage as the covariance can be discarded from the evaluation [17]. For complex non-linear models, a Monte Carlo based method can be used [17]. The latter method uses repeated calculation of the output, while varying the input [18]. In a first step, all sources of uncertainty should be identified, whereas in the next step these uncertainties should be quantified [19]. The uncertainty limits can be based on the measurement error of the used sensors, or by using previously quantified confidence intervals. The input is then randomly selected from its error Probability Density Function (PDF) using a sampling scheme (e.g. random or Latin Hypercube). The calculated outputs will also be distributed, which allows defining an output uncertainty distribution. The drawback of the Monte Carlo method is the number of iterations (i.e. Monte Carlo shots) that should be carried out (in the order of hundreds to thousands depending on the number of sources of uncertainty considered) before the variance of the output distribution is known accurately [18]. This makes the technique computationally expensive, especially for complex models.

2. Problem statement and objectives

As indicated in Section 1.1 process monitoring is mostly done by using off-line time-consuming measurements or by implementation of extra sensors. The automatically collected in-line real-time univariate data is nowadays logged, but is typically not used for process monitoring and/or controlling.

The main objective of this work is the use of a combined mass and energy balance to estimate the moisture content of granules at the end of the drying process in a six-segmented fluidized bed dryer, being part of a full continuous pharmaceutical from powder-to-tablet manufacturing line. The energy balance is made to compare the experimental gas outlet temperature with the calculated one as a validation of the balances. In the calculations error propagation will be accounted for in order to consider uncertainty. Once the balances are validated a prediction of the gas temperature in different horizontal sections of each drying segment can be

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