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Title: Process monitoring of a full continuous pharmaceutical tabletting line: Mass & energy balance analysis

Abstract:

Nowadays, pharmaceutical production processes are undergoing major changes, and there is a clear trend towards increased use of continuous production processes [1]. The focus of our ongoing work is on the formulation of the Active Pharmaceutical Ingredients (APIs) into final drug products. The evolution from batch to continuous production is also of increasing interest in formulation operations [2-3]. Whereas in traditional batch processes product quality evaluation mostly relies on off-line, time-consuming and, hence, less efficient laboratory testing [4], the continuous approach possesses clear advantages as the efficiency can be improved by relying on in-line measurements and real-time adjustment of sensitive process variables. Monitoring and controlling the process during operation can be much more economical through significant decreases in product loss [4-5]. By using the on-line monitoring to support the implementation of real-time release in the production of pharmaceutics, pharmaceutical companies does not have to wait anymore till the product is approved by the quality lab.

The ConsiGma™ (Collette™, GEA Pharma Systems, Wommelgem, Belgium) is a continuous from-powder-to-tablet manufacturing line intended for tablet production. The continuous line consists of three parts: a continuous twin screw granulator (high shear), followed by a six-segmented fluidized bed dryer system and a discharge system prior to the tabletting press. During continuous operation a large number of process variables are continuously logged. These variables can be used by the operator to verify smooth process behavior. However, they can be analysed in more detail as well, in order to improve process operation. In this contribution, a mass and energy balance verification over the fluidized bed dryer unit is performed, which provides further insight in the process.

The mass balance can be used to calculate the moisture content at the end of the drying process. As such, by making a mass balance a time-consuming off-line Karl Fisher titration could be avoided or done on a less regular basis. The mass balance is based on the changing properties of the drying air passing the dryer unit from inlet to outlet and accounts for the evaporation process. The energy balance is interesting for two reasons; it can be used to compare the measured gas outlet temperature with the calculated value based on logged variables. A good match between prediction and measurement will increase trust in the correctness of the mass balance, and demonstrates process understanding. On the other hand the energy balance can be helpful to predict the gas temperature in different horizontal sections of the drying system. This information is useful to combine in a later stage with information about the trajectory of granules through the system. The fluidization behavior is investigated in another part of the project using Computational Fluid Dynamics (CFD). The CFD-model can give information about the bed height of the fluidized bed; evaporation of water only takes place in this part of the dryer, which is the most determining factor for the gas temperature. The temperature profile will be based on several model assumptions, which is acceptable since experimental measurements are time-consuming and laborious.

Experimental data revealed that a calibration was needed in order to calculate the evaporation rate as a consistent offset between prediction and measurement occurred. A linear regression was implemented in the model to quantify this offset. A linear error propagation of measurement errors was pursued to account for their effect on output uncertainty.

Based on several datasets, it can be concluded that it is indeed possible to use the standard logged measurements to monitor the process. As such, an important conclusion is that expensive probes (e.g. NIR [6]) are not always needed to implement in the final production system. However, they are still extremely useful in process development to support development of detailed process knowledge.

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