

REPRINT TESTING PAT UNDER REALISTIC CONDITIONS

Determining the drying endpoint in fluidized bed processes

Facts for the decision-makers

- » Online analysis procedures should help put the PAT concept into practice.
- » A moisture sensor allows the endpoint of a drying process in a fluidized bed machine to be determined by ascertaining the moisture content of the product being dried while it is still being processed.
- » In addition, the sensor also provides information about the homogeneity of moisture in the product.
- » Online analysis can be tested in the new Innovation Center in Binzen and customized for each specific case.

Industry		Function	
Pharma	● ● ●	Planner	● ● ●
Food	● ● ●	Operator	● ● ●
Cosmetics	● ● ●	Purchaser	● ● ●
Chemistry	● ● ●	Manager	● ● ●



The online moisture technology allows to determine the endpoint of drying process in the fluidized bed without taking samples.

Whatever the process, whether conti or batch: Process Analytical Technology (PAT) and parametric release are currently the hottest topics in pharmaceutical technology. One example of PAT is determining the drying endpoint in fluidized bed processes. The installation of online moisture sensors makes a whole lot of sense.

In previous pharmaceutical practice, determining whether a product is dry enough or not was mostly done with an offline analysis of moisture and the temperature of the product or exhaust air. This procedure leaves considerable room for improvement since offline analysis requires additional time and since the temperature measurement can only be performed indirectly. If the product



Tews sensor provides also information about the homogeneity of moisture in the product.

has not reached the required residual humidity, additional costs will be incurred by restarting the process. Pharma companies can accelerate the process significantly by using an online moisture measurement system. Furthermore, an online moisture measurement system increases process safety in the production routine.

Christian Knopf, a project manager for new technologies employed by the pharmaceutical plant engineering company Glatt, is currently focusing on the optimization of the drying process in the fluidized bed.

He affirms: "The aim has to be to achieve maximum cost efficiency. Other industries prove that PAT can do that." One of the things Christian Knopf is investigating is

online analysis, which will help in turning PAT theory into practice: suitable measurement and analysis methods assist with the controlling of pharmaceutical production, to allow the release of products without the laborious quality control of the final product. According to the PAT initiative, so-called parametric release is possible when previously-defined, quality-relevant parameters in the process are monitored and are documented within to be within target specifications.

To determine the endpoint of drying processes in the fluidized bed, the plant engineering company uses an online moisture sensor made by Tews Elektronik, not only in its GMP laboratory but also in its new Innovation Center in Haltingen, close to Binzen in southern Baden, Germany. Using this sensor provides two clear benefits, as it not only tests the moisture content of the product to be dried while the product is still being processed, it also provides information about the homogeneity of moisture in the product. "The sensor's microwave field allows us to look directly into the product", explains Christian Knopf. The microwave sensor penetrates the deposited product to a depth of up to 50 mm and takes moisture measurements from the particle cores. As opposed to other methods of measurement, such as NIR, the online procedure is totally unaffected by dust accumulation on the sensor. Another benefit is that there's no more need for labor-intensive multivariate data analysis, which substantially accelerates the calibration process. A measurement frequency of 10,000 values per second means that any changes in humidity are quickly registered, too.

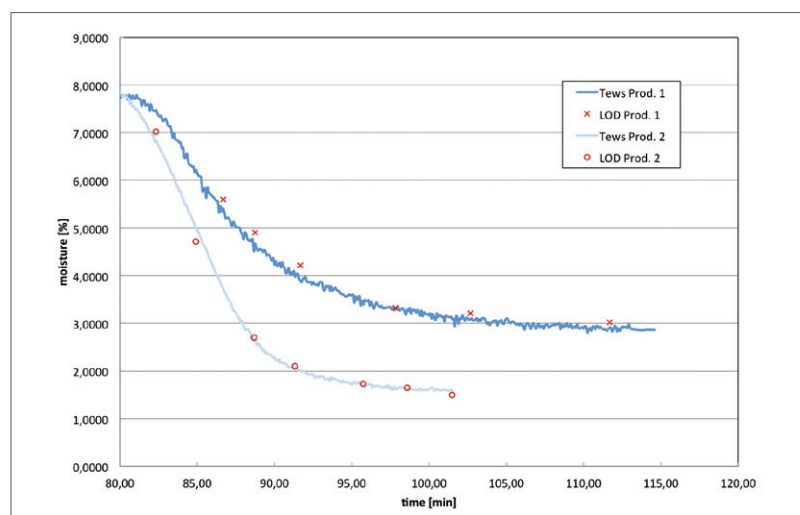
The PAT Sensor is customized for the specific requirements of the technical center.

To ensure that the sensor technology really is suitable for PAT in a later process, the experts modify the online analysis according to the products and the requirements of the pharmacists. The Innovation Center, which opened in Fall 2016, is the testing environment where topics such as optimum dryer configuration and ideal arrangement of the sensors in the fluidized bed machine are examined. For example, it is important – particularly with batch processes – to ensure that the sensor remains constantly submerged in product during drying, even when using a minimum load. Christian Knopf sees the largest potential for use in the optimization of the production process: "by using online moisture measurement, we are able to shorten release times for products by a significant margin." Glatt's Head of Marketing, Axel Friese, adds that "pharmacists who are considering the integration of online analytics into their processes can use our testing environment to examine whether online sensor technologies yield identical or even better results than previous offline monitoring methods." Despite the fact that the integration of new technologies into



Christian Knopf, a project manager for new technologies employed by Glatt.

Comparison of online moisture measurement (blue lines) and offline methods (red points/crosses).





Axel Friese is Head of Marketing at Glatt.

“Pharmacists who are considering the integration of online analytics into their processes can use our testing environment to examine whether online sensor technologies yield identical or even better results than previous offline monitoring methods.”

existing processes is rather uncommon in the pharmaceutical world, the specialists from Haltingen are convinced that upgrading even established processes with online analytics is money well spent. If one looks at worldwide globalization, products which are outsourced to other locations are certainly able to benefit from PAT. PAT speeds up process validation and allows the market launch of a product to happen much sooner. Integrating PAT into a process is even worthwhile with a new product or a scale-up.

But what contribution can the online system make to parametric release? According to Christian Knopf, simply replacing offline measurement with the online system can bring time savings of up to 20 minutes per batch. In addition, further important minutes can be saved by optimizing the process, e.g. by shutting down earlier. Pharmaceutical companies only have to calculate how many batches need to be performed per year to realize how worthwhile it is to invest in this kind of technology. It is important that extensive tests are performed to find out how much time can be saved in each individual case.

Process optimization in the new Innovation Center

In Fall 2016, Glatt inaugurated a new Innovation Center in Binzen, Germany.

The 7000 m² premises allow customers to optimize their products and procedures with batch and conti processes and the use of analysis technology. The flexibility of the batch-based machines allows them to be configured as needed for granulation, pelletization and coating processes, from laboratory to production scale with batch sizes of up to 150 kg. The new MODCOS process machines allow powders to be continuously processed right up to the finished tablet. A whole range of modular processing equipment is available that can be arranged into a fully-automated process line. Modular process lines enable the use of processing options from direct compression to wet granulation. Our own GlattView Conti control system allows the process to be controlled by PAT measurements at the appropriate places and provides complete documentation of the process.

Integration in batch and conti processes.

Online moisture measurement is integrated into both batch processes and conti machines with the manufacturer's own in-house control systems known as Glatt Mega, Eco and Conti, which conform to the requirements of 21 CFR Part 11. The necessity for quick control using PAT methods is particularly important in continuous processes, considerably more so than in batch processes. The measured value for moisture plays a major role and is an essential parameter for the monitoring of drying quality. This value is displayed in a flow chart by the control system and can be used as both a monitoring parameter and a shutdown criterion.

Christian Knopf explains that “the Tews sensor works with product moistures of up to 7 %, with a precision of 0.1 to 0.2 % – absolutely sufficient for determining the drying endpoint.” However, he adds that “it would be nice to have a larger measuring range and be able to monitor the whole granulation process”. The specialist also sees room for improvement in the measurement method, which compensates for fluctuations in density: “In future, it will be possible to calibrate to the density of the bulk. This will allow granulates to have their densities optimized for later tableting, sieving and transport.” Knopf is convinced that the use of process analytical technologies is the key to successfully implementing Quality by Design (QbD) in continuous and discontinuous production processes.

We offer our customers the potential to make their processes even more efficient and cost-effective with the implementation of field-tested PAT solutions.