# In-line measurement of granule water content in a fluidized bed dryer using microwave resonance technology as a novel PAT tool

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## Introduction

Process analytical technologies (PAT) are to be implemented in modern drug development and manufacturing processes as demanded by the U.S. drug regulatory office FDA [1]. Today, only a few analytical technologies, e. g. near-infrared spectroscopy (NIR), are available to meet the FDA requirements. The key problem in the drying process of solid particulates, like granules or pellets, is the control of the solvent residuals and in particular, the water content or moisture of the granules. In the past, there have been some attempts to control the moisture of granules in a fluidized bed dryer by NIR and also microwave absorption. However, the results have been rather disappointing. The NIR absorption depends on the total amount of measured particle layers and the density of the fluidized bed and therefore cannot be directly correlated with the water concentration in the granules. Microwave resonance technology is a relatively new technique, already used in food technology, that enables the measurement of both the total amount of water and simultaneously, the powder density by the shift of the wavelength to a lower frequency (Fig. 1).

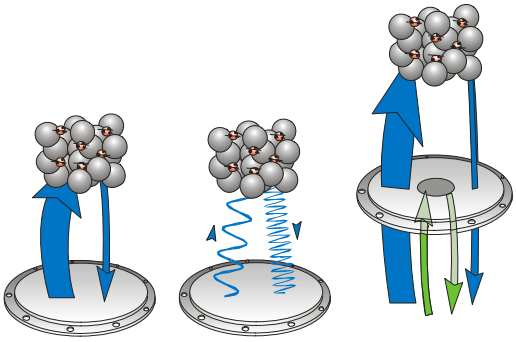

Fig. 1: Principle of the determination of particle moisture by the novel microwave resonance sensor.
Left: Absorption of microwaves by water molecules
Middle: Frequency shift of microwaves by particulates
Right: Correlation of the signals to a reference sensor in the center

## Experimental methods

*Preparation of granules*

Powder blends consisting of 2 kg Microcrystalline Cellulose, MCC (Vivapur 101, JRS Pharma, Rosenberg, Germany) and 4 kg Lactose (Granulac 200, Meggle, Wasserburg, Germany) were mixed in the high-shear granulator FM-VG-25P (Powrex, Hyogo-Ken, Japan). Wet granulation was performed using 1.7 kg aqueous solution of 10 % (m/m) Povidone 90 (Kollidon 90 F, BASF, Ludwigshafen, Germany) as a binder. Prior to the fluid bed drying operation, the wet granules were passed through a 5 mm square hole wet sieve (GS 180, Glatt, Binzen, Germany). The applied processing parameters are given in Tab. 1.

| Process operation | Impeller Speed [rpm] | Chopper Speed [rpm] | Time [min] |
|---|---|---|---|
| Dry mixing | 200 | off | 1 |
| Binder dosage | 200 | low | 6 |
| Granulation | 400 | low | 3 |

Tab. 1: Parameters of the high-shear granulation process.

*Drying of granules*

The wet granules are manually transferred into the fluid bed dryer GPCG 15 (Glatt, Binzen, Germany) that was equipped with the new microwave resonance sensor MoistureScan (Döscher & Döscher, Hamburg, Germany). The product bowl was equipped with a standard 100 µm PZ bottom sieve plate. The inlet air temperature and volume were varied (Tab. 2). Routinely, the inlet air volume was adjusted to 1200 $m^3$/h. The dew point of the inlet air was 14.2 ±0.6 °C (n=3).

| Process operation | Minimum | Maximum |
|---|---|---|
| Inlet air temperature [°C] | 45 | 65 |
| Inlet air volume [$m^3$/h] | 0 | 1700 |

Tab. 2: Parameters of the drying process.

*Off-line determination of residual water*
The water content of the granules was determined off-line by measuring the loss on drying (LOD) using the heat balance LJ16 Moisture Analyzer (Mettler Toledo, Gießen, Germany). The temperature was set to 70 °C, the end point detection was performed in the automatic mode.

*On-line monitoring of residual water*
The granule moisture was monitored during the drying process by the MoistureScan sensor (Döscher & Döscher, Hamburg, Germany). The sensor was installed into the lower-third section of the product container instead of a sight glass window (Fig. 2). Due to the mounting position the sensor is in contact with sufficient amount of granules throughout the complete drying process.

Fig. 2: Mounting position of the MoistureScan sensor (arrow) at the fluidized bed dryer.

**Results and discussion**
To confirm the independency of the measured water content from the powder density, pre-dried granules were subjected to the dryer and the inlet air volume was increased at discrete levels (Fig. 3). If the measured water content would correspond with the amount of particles in the focus of the sensor, the moisture signal must dramatically decrease when increasing the inlet air volume. However, using the new microwave resonance sensor the determined moisture was independent from the inlet air volume and hence, the powder density.

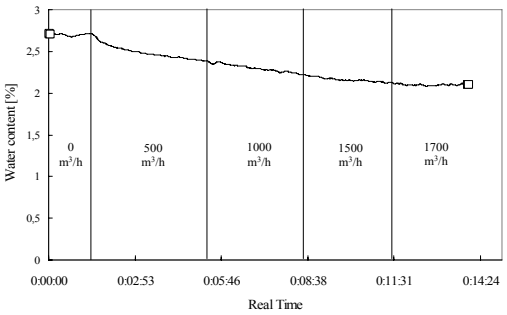


Fig. 3: Water residuals in granules measured at different inlet air volumes of the dryer.

Various batches of the lactose-MCC granules with Povidone 90 as a binder were monitored during the drying process by the MoistureScan sensor. The water content in the granules, calculated by the microwave absorption and the shift of frequency, and the temperature at the sensor surface were continuously registered. The measured water content of the granules was compared to the LOD of samples withdrawn discontinuously from the batch. In all batches, the measured in-line granule moisture correlated well with the LOD. Two examples of the track and the related LOD results are displayed in Fig. 4.

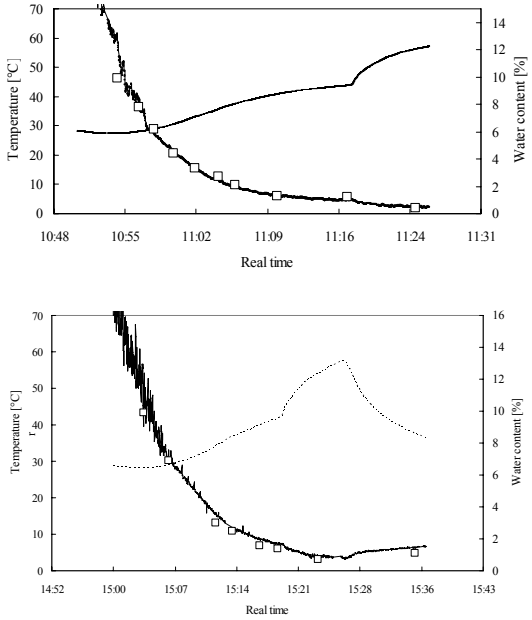


Fig. 4: Water residuals in granules in-line monitored by the MoistureScan sensor and correlating LOD results (□).

**Conclusions**
The newly developed microwave resonance sensor is a reliable PAT tool for continuously monitoring of the water content in particulates during a fluidized bed drying process. The measured values are precise and correlate with the results of an external loss of drying method. After full validation, the sensor could replace the off-line determination of water content. Drawing samples from the granule batch is not necessary any longer. The drying process can be continued until the pre-fixed end-point without any discontinuation. We are now going to test the new sensor in granulation and coating processes.

**References:**
[1] Food and Drug Administration, Process Analytical Technology Initiative, Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance http://www.fda.gov/Cder/OPS/PAT.htm