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Research paper

In-line monitoring of granule moisture in fluidized-bed dryers using microwave resonance technology

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Abstract

This is the first report on in-line moisture measurement of pharmaceutical products by microwave resonance technology. In order to meet the FDA's PAT approach, a microwave resonance sensor appropriate for pharmaceutical use was developed and implemented into two different fluidized-bed dryers. The novel sensor enables a continuous moisture measurement independent from the product density. Hence, for the first time precise real time determination of the moisture in pharmaceutical granules becomes possible. The qualification of the newly developed sensor was performed by drying placebo granules under experimental conditions and the validation using drug loaded granules under real process conditions. The results of the investigations show good correlations between water content of the granules determined by the microwave resonance sensor and both reference methods, loss on drying by infrared light exposure and Karl Fischer titration. Furthermore, a considerable time saving in the drying process was achieved through monitoring the residual water content continuously by microwave resonance technology instead of the formerly used discontinuous methods.

Keywords: Process analytical technology; Microwave resonance technology; Moisture measurement; Granule water content; Fluidized-bed dryer; Wet granulation

1. Introduction

The United States' Food and Drug Administration (FDA) requests the implementation of process analytical technologies (PAT) in modern drug development and manu-facturing processes. The goal of the PAT initiative is to ensure the final product quality [1]. In this context the term PAT summarizes analytical systems and methods for continuous analysis and monitoring of critical process and quality parameters of raw materials and in situ products [2].

In wet granulation processes the residual water content of the granules is a critical product parameter which has a significant influence on the finished product quality, e.g. the stability of the active pharmaceutical ingredient (API), the granule hardness and homogeneity. Furthermore, the moisture of granules affects subsequent process steps like tabletting, where wet granules may lead to poor flow properties. It is obvious that an exact end-point determination of the drying process is of major importance to ensure the quality of the drug products.

So far, the methods of water content determination like Karl Fischer titration, loss on drying (LOD), loss on drying using infrared light (LOD/IR), nuclear magnetic resonance

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spectroscopy (NMR) do not fully meet the requirements intended by the PAT approach. By sample withdrawal and external analysis these methods are associated with a loss of time and it is impossible to obtain real time control of the drying process. In general there are three possibilities to control the moisture in a fluidized-bed process: (1) the drying process runs discontinuously by discontinuous sample withdrawal, (2) a continuous process is monitored by discontinuous sampling, and (3) the granule moisture is recorded continuously in a continuous drying process.

Up to now there have been only few analytical technologies available for the in-line determination of moisture in dried powders or granules. There have been several attempts to make use of NIR spectroscopy in moisture control [3–6]. Due to the short wavelength and thereby existing high reflection of radiation a depth of penetration in the fluidized bed is not available. This implicates that only the surface moisture of the material can be determined. Since the near infrared sensor is mounted by a window flush to the wall, further problem arise by particle layers on the measuring window. This leads to reflection of the radiation, making a moisture measurement impossible or insecure [7]. Further, microwave absorption was used to monitor the water content of granules in a fluidized-bed dryer. Wetting of granules was determined by a one-parameter measurement as a function of the total product moisture [7]. The methods used so far have significant limitations. Both, the NIR absorption and the microwave absorption strongly depend on the total amount of measured particle layers and the powder density of the solid material. Therefore, the signals cannot be directly correlated with the water content of the particles and may vary during the process. An analytical method that is independent from both the particle density and the powder bed density is a prerequisite for the precise in-line control of product moisture in fluidized-bed dryers.

Recently, microwave resonance technology (MRT) has been established in food industry. This new technology enables continuous, density independent moisture monitoring of solid products, e.g. on conveyor belts [8]. The rationale for using MRT is the access of both the total water amount and the powder density by a single and simultaneous measuring procedure. Before external stimulation, the water molecules are disordered within the solid particles. In conventional microwave technologies, the water molecules become aligned in accordance with the polarity of the electromagnetic field induced by the frequency of a suitable microwave. If the electromagnetic field changes its polarity very fast, only water molecules are able to follow because of their large dipole moments and their small molecular masses. For each turnaround a loss of energy can be determined that is disposed from the electromagnetic field. Hence, the energy correlates with the total amount of water molecules in the medium [9]. However, the total amount of water measured in the analysis width does not give an appropriate indication of the water content in the dried particles as the signal does not reflect the powder density. In contrast, MRT is a two-parameter measurement that offers combined determination of the energy loss by microwave absorption caused by water molecules and the powder density by a shift of the wavelength of the applied microwaves as described in the methods section in detail.

The purpose of our study was to employ MRT in monitoring the moisture of granules in Glatt fluidized-bed dryers. Therefore, a new sensor system had to be developed that enables the in-line determination of water in the solid particles during the drying process and that is in accordance with the current guidelines of Good Manufacturing Practices (cGMP). Furthermore, the practical application of the mounted MRT sensors should be investigated under test and real process conditions in pharmaceutical processes.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (MCC) was used in the Vivapur® 101 (JRS Pharma, Rosenberg, Germany) and in the Avicel® PH 101 (IMCD Deutschland, Köln, Germany) qualities. α-Lactose monohydrate (Granulac 200®) was obtained from Meggle (Wasserburg, Germany). Povidone 90 (Kollidon 90F®) was purchased from BASF (Ludwigshafen, Germany). Hydranal® Coulomat AG, Hydranal® Coulomat EG (Riedel-de Haën, Seelze, Germany), dried methanol, sodium tartrate dihydrate (Merck, Darmstadt, Germany) and pure nitrogen (Air Liquide, Krefeld, Germany) were used as Karl Fischer titration reagents.

2.2. Microwave resonance technology

The microwave resonance technology utilizes the interaction between water molecules and changing electromagnetic fields. The measuring frequency of the employed stray field sensor is predetermined by the resonance wavelength of the microwave inducing resonator. The resonance frequency depends on the geometries of the employed sensors. If the resonator is loaded with materials, an increasing storage of electric field energy can be observed which leads to a decreasing resonance frequency. The permittivity, which gets excited by the storage of energy, significantly changes in relation to the water content. In addition, the wet material disposes energy of the resonator, which results in an increasing width of the resonance waves. Since resonators respond very sensitively, a high accuracy of measurement is possible. While an increasing water burden leads to a decreasing resonance frequency, the frequency band width broadens simultaneously (Fig. 1). The broadening of the detected resonance frequency band is caused both by the product moisture and by the material load in the focus of the sensor. By considering frequency and band width simultaneously and comparing it to the unstressed resonator in air, two independent properties become available, which enable the determination of two product

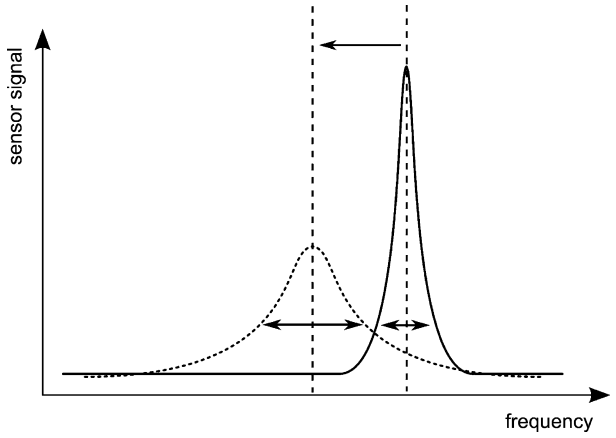

Fig. 1. Microwave resonance curves. With increasing water content the microwave resonance frequency decreases, while the frequency band width increases. (▬) Resonance curves in air (empty sensor). (·····) Resonance curve in wet material (loaded sensor).

parameters, the density and the moisture. Therefore, a density revised moisture measurement, or vice versa, a moisture revised density measurement can be obtained. The moisture Ψ refers to the total amount of water molecules in the sensitive measuring area:

$$\Psi = \frac{m_W}{m_W + m_d} \quad (1)$$

where m_W symbolises the mass of water molecules and m_d the mass of the dry material [10,11]. Both, the decrease of the resonance frequency (Δf) and the magnification of the band width (ΔB), depend on the material density, but to a different extent on the water content (Ψ) in the sensitive field of the resonator. By calculating the ratio of band width magnification and decrease of resonance frequency it is possible to eliminate the influence of the solid particle density:

$$M(\Psi) = \frac{\Delta B(\Psi, m_{tot})}{\Delta f(\Psi, m_{tot})} \quad (2)$$

Thus, the moisture function ($M(\Psi)$) is only a function of the moisture content [11]. Due to the fact that microwaves are able to permeate the product, the physically bound water is recorded completely. In contrast, crystal water is not monitored as this would require different wavelengths and intensities of the applied microwaves. Due to the thermal expansion of the resonator the resonance frequency also depends on the temperature. Caused by energetic loss in metallic walls and, respectively, by the so-called skin effect, the band width depends on the temperature as well [10–12]. However, preliminary investigations on microwave resonance sensors have shown that in most cases the influence of the temperature of the used resonator is negligible [11]. According to the literature MRT is almost independent from the colour or UV absorption of the product, the conductivity, the characteristics of particles and from inhomogeneous distribution of water molecules within the material [13]. Furthermore, warming of the monitored product does not occur since MRT operates at low energy of less than 10 mW [14]. Therefore, an impact of the measurement on the stability of the product is very unlikely.

2.3. Stray field resonance sensor

The stray field resonator Hydorpharm® (AMS Advanced Microwave Systems GmbH, Elmshorn, Germany) was developed within the present study (Fig. 2) and has been mounted to GPCG 15 and WSG 60 fluidized-bed dryers, both from Glatt GmbH (Binzen, Germany). A stray field resonator represents an open resonator with an external electric stray field, which extends into the product space. The analytical method works without any distance adjustment, which results in a considerable enhancement of measurement accuracy and offers an universal utilization. The tested material may be irregularly distributed on the surface and the relevant area above the stray field sensor [15]. The mounted stray field resonator consists of a dielectric ceramic wave guide, which has a ring-shaped conformation and is soldered in a disc made from titanium (Fig. 2). The chosen materials and surfaces are suitable for the use in pharmaceutical processes and are in accordance with cGMP guidelines. An electronic unit is incorporated in the resonator. The stray field resonator works at 2.5 GHz, which is a free ISM (industrial, scientific and medical) band, generating a prefixed electromagnetic field. By inserting wet materials into the electromagnetic field, the resonator frequency undergoes changes as described before (Fig. 3a and b). In order to verify a complete compensation of the covariates, an independent reference unit was incorporated in the sensor (Fig. 3c). This leads to an improved precision and repeatability [12]. As the signals from the microwave resonance sensors depend on the absolute temperature in general, the temperature was measured directly under the sensor‘s surface by a PT 100 thermo sensor. Since preliminary investigations have shown that the influence of the temperature on the used sensor [11,12] is often negligible, and that the temperature range of the fluidized-bed drying process is very narrow, the temperature signals were not used to correct the calculated water content of the granules within the present investigations. However, the measured temperatures under the sensor surface were considered as a further parameter that enables a better understanding

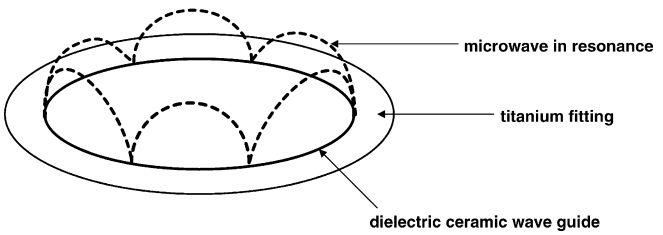

Fig. 2. Setup of the new stray field resonator developed for the study.

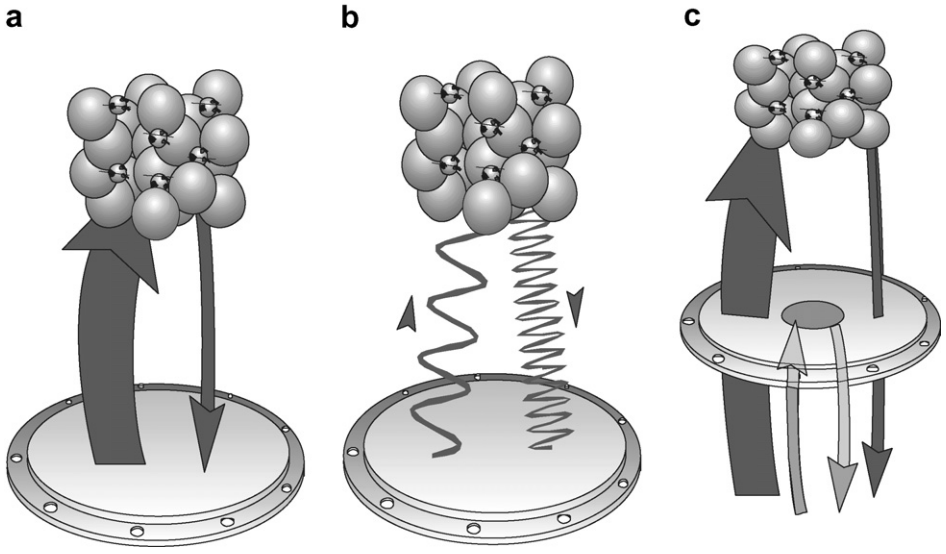

Fig. 3. Principle of the determination of product moisture by the microwave resonance sensor. (a) Absorption of microwaves by water molecules. (b) Frequency shift of microwaves by particulates. (c) Correlation of the signals to a reference sensor in the centre.

of the process. The received measuring values for moisture, density and temperature were analyzed electronically and evaluated by the provided software MWF-Standard (Döscher & Döscher, Hamburg, Germany).

2.4. Drying of placebo granules

In the high-shear mixer FM-VG-25P (Powrex, Hygo-Ken, Japan) powder blends consisting of 33% of microcrystalline cellulose, MCC (Vivapur® 101, JRS Pharma, Rosenberg, Germany) and 67% of α-lactose monohydrate were mixed. Wet granulation was performed using 1.7 kg aqueous solution of 10% (m/m) povidone 90. The batch size was 6 kg. After passing the wet granules through a 5-mm wet sieve (GS 180, Glatt GmbH, Binzen, Germany), the wet granules were manually transferred into the fluidized-bed dryer GPCG 15 (Glatt GmbH, Binzen, Germany) equipped with a standard 100 μm PZ bottom sieve plate and the newly developed Hydorpharm® sensor. Since the GPCG 15 operates with a double chamber filter system, an uninterrupted process is ensured even when cleaning the filter. The inlet air of the fluidized-bed dryer was not conditioned. A summary of the test conditions and parameters is given in Table 1.

The drying process was monitored continuously by using the novel sensor and discontinuously by already established methods. At predefined time points samples of approximately 4 g were withdrawn and externally analyzed by determination of loss on drying using infrared light exposure and a weight balance. The recorded in-line signals were compared to the off-line measured water content of the samples.

2.5. Drying of verum granules under real process conditions

Powder blends consisting of 16% API water-free crystals and 84% of MCC (Avicel® PH 101) were mixed in the fluidized-bed granulator WSG 60 (Glatt GmbH, Binzen, Germany) equipped with the newly developed Hydorpharm® sensor until reaching a product temperature of approximately 38 °C. Afterwards the wet granulation started using 17.4 kg aqueous solution of 7% (m/m) Povidone 90. As soon as the granulating fluid was completely applied, the drying process of the wet granules was started. The batch size was 53 kg. The fluidized-bed dryer uses a one-chamber system. Therefore, the process gets interrupted for a few seconds during cleaning of the filters by vibration move-

Table 1
Synopsis of experimental conditions and parameters for the drying processes of placebo and verum granules

Granule type	Composition of granule	Composititon of granulating fluid	Fluidized-bed dryer	Inlet-air temperature (°C)		Inlet-air volume (m^3/h)		Moisture:in-line monitoring	Moisture:reference methods
				Min	Max	Min	Max		
Placebo granules	33% MCC 101 67% lactose monohydrate	Aqueous solution of 10% povidone 90	GPGC 15	45	65	0	1700	Microwave resonance sensor (Hydorpharm®)	LOD/IR (70 °C)
Verum granules	84% MCC 101 16% API (water-free)	Aqueous solution of 7% povidone 90	WSG 60	60	65	1100	1341	Microwave resonance sensor (Hydorpharm®)	1. LOD/IR (100 °C), 2. Karl Fischer titration

ments. A summary of the experimental conditions and parameters is given in Table 1.

The drying process of the primarily produced granules was monitored discontinuously according to the current specification of the marketed drug product. At defined time points the drying process was interrupted to withdraw samples of approximately 4 g mass and to determine the loss on drying using infrared light and a weight balance. Additionally, the granule water content of the samples was determined by Karl Fischer titration. Simultaneously, the MRT signals were recorded and compared to the off-line data on residual water. The drying process of another verum granule batch was not interrupted for withdrawal of samples, but continuously monitored by the microwave resonance sensor and stopped when the specified moisture limit was reached.

2.6. Karl Fischer titration

The moisture content of the verum granules was measured using the Moisture Meter® CA05 with dry heat oven VA05 (Mitsubishi Chemical Industries Limited, Tokyo, Japan). Further, the analytical balance Mettler AT261® (Mettler-Toledo GmbH, Gießen, Germany) was used. After weighing the sample in an aluminium crucible the moisture was expelled heating at 170 °C and led over by nitrogen flow to the measuring cell, in which the water determination was carried out.

2.7. Loss on drying by infrared light

The water content of the placebo granules was determined by measuring the loss on drying caused by infrared light (LOD/IR) using the heat balance LJ16 Moisture Analyzer® (Mettler Toledo, Gießen, Germany). The temperature was set to 70 °C and the end-point determination was performed in the automatic mode.

During the drying process of the verum granules the residual water was determined by measuring the LOD/IR using the heat balance MA 45 Moisture Analyzer® (Sartorius AG, Göttingen, Germany). Due to the higher amount of MCC in the verum samples the temperature was set to 100 °C. The end-point determination was performed in the automatic mode.

3. Results and discussion

3.1. Qualification of the new sensor

To qualify the newly developed MRT sensor, a batch of placebo granules was subjected to the fluidized-bed dryer equipped with the sensor mounted at the lower part of the product container (Fig. 4). The sensor with a smooth surface was integrated flushing with the inner surface of the product container. Therefore, disruption of the granule flow pattern is unlikely and has not been observed. At given time points granule samples were withdrawn and

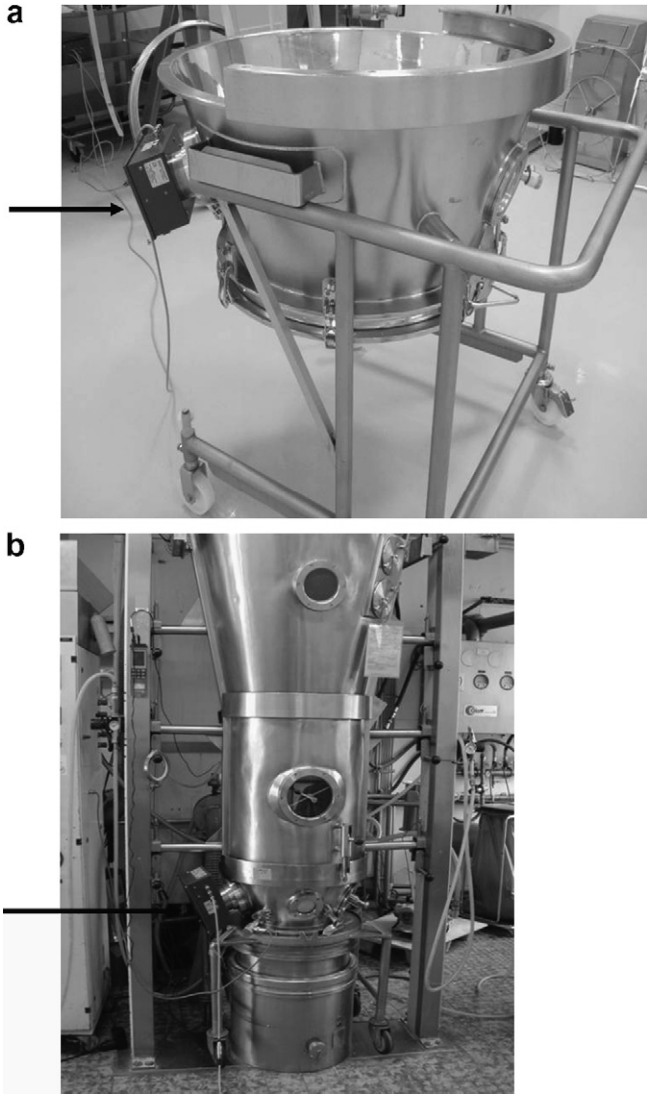

Fig. 4. MRT Hydorpharm® sensor mounted at two different Glatt fluidized-bed dryers (see black arrows). (a) WSG 60 (b) GPCG 15.

the water content was determined by LOD/IR. The obtained results were used to calibrate the sensor by calculating granule-specific correction factors using the delivered software. The obtained calibration factors were used in all subsequent experiments of placebo granules.

Fig. 5 displays the moisture track throughout the drying process of a lactose-MCC placebo granulate continuously monitored by the MRT sensor. At the beginning of the drying process the granules contained a water content of approximately 18%. After a drying time of approximately 37 min the moisture of the granules was 0.4%. For evaluation of the MRT method, the determined water content of the granules was compared to samples withdrawn discontinuously from the batch and analyzed off-line by LOD/IR. The determined in-line and off-line moisture of the granules correlated well at moisture levels below 10%.

In order to investigate the repeatability of these results, various batches of placebo granules with the same composition were monitored at similar processing conditions. The

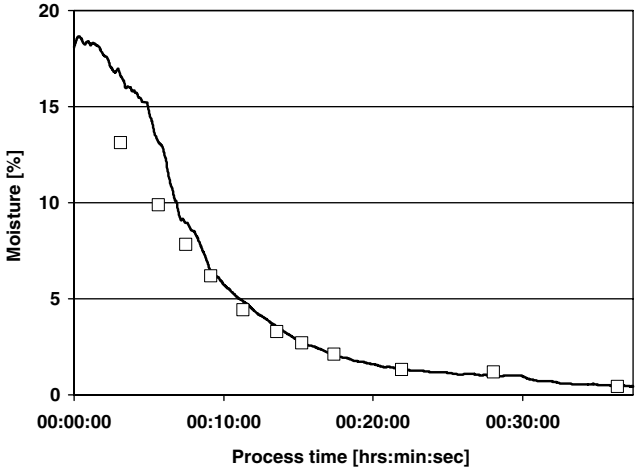

Fig. 5. Moisture (%) in placebo granules during the drying process in GPCG 15. (▬) Signal from microwave resonance sensor. (□) Loss on drying by infrared light exposure (LOD/IR).

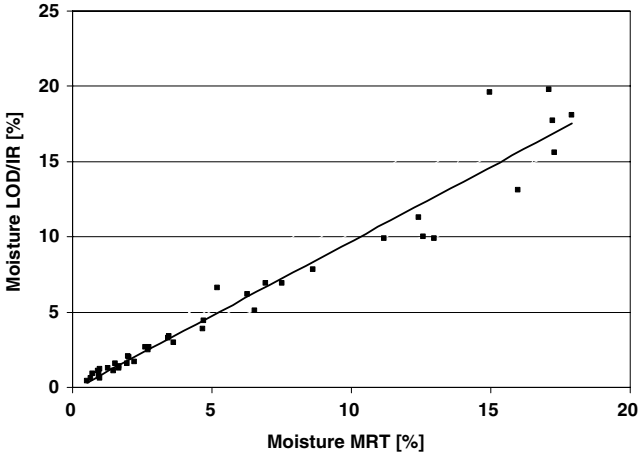

Fig. 7. Correlation of moisture values from loss on drying by infrared light exposure (LOD/IR) and from microwave resonance technology (MRT). (▬) Regression line, $r = 0.976$.

results of the continuous in-line moisture measurement and the discontinuous off-line water determination are given in Fig. 6. Since the GPCG 15 operates with unconditioned inlet air, differences of the granule moisture between 16% and 19% were recorded in the initial phase of the drying process. The moisture values of the granule batches became very similar in the ongoing process. At the end of the drying the curves were almost superposed (Fig. 6). In all batches the water content of the granules correlated well with the results obtained by LOD/IR. The correlation of the water content measured by MRT sensor and the moisture determined by LOD/IR is shown in Fig. 7, plotting the determined LOD/IR values against the MRT moisture. The linear regression coefficient is 0.976. Mainly in the section of a low water content, which is crucial for the end-point monitoring of the residual water content in the fluidized-bed drying process, a very good correlation between both methods was achieved. A conceivable reason for higher deviations between the two methods in the range of high granule moisture could be the different fraction of bound and unbound water. Further investigations will focus on this issue.

3.2. Independency from product flow density

In order to verify the independency of the measurement suggested by MRT theory, pre-dried granules were subjected to the fluidized-bed dryer GPCG 15. The inlet air volume was varied at predefined time points at discrete levels. Thus, the inlet air volume was adjusted to 500 m^3/h in the initial phase and then stepwise increased up to 1700 m^3/h in the last section of the drying period (Fig. 8). If the sensor output signal would be affected by the amount of particles in the focus of the sensor, the moisture signal is expected

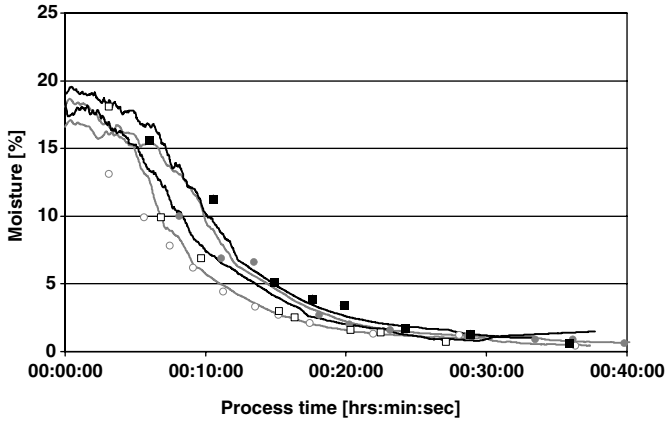

Fig. 6. Repeatability of moisture (%) measurement in placebo granules during drying processes in GPCG 15. (▬) Microwave resonance sensor, batch 1. (▬) Microwave resonance sensor, batch 2. (▬) Microwave resonance sensor, batch 3. (▬) Microwave resonance sensor, batch 4. (○) LOD/IR, batch 1. (●) LOD/IR, batch 2. (■) LOD/IR, batch 3. (□) LOD/IR, batch 4.

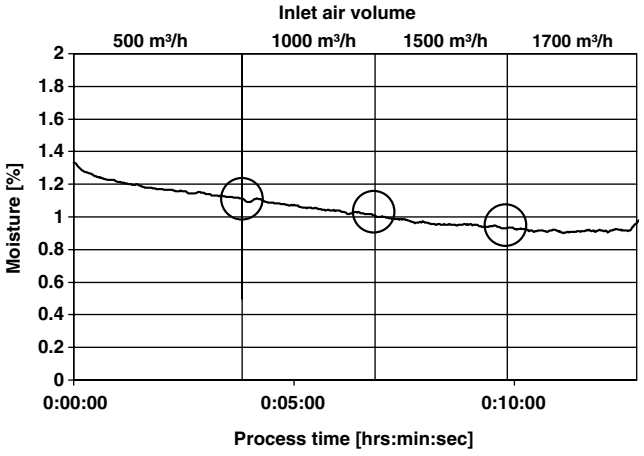

Fig. 8. Independency of flow density on measured granule moisture using the novel microwave resonance sensor in GPCG 15. (▬) Microwave resonance sensor signal. (○) Time-point of rapidly changing the inlet air volume (500 to 1700 m^3/h).

to dramatically decrease when increasing the inlet air volume. In our investigations such an effect was not observed. Only a slight, hardly remarkable decrease of the moisture from 1.3% to 0.9% was recorded, which can be attributed to a residual drying in the pre-dried granules. Hence, the new MRT sensor acts independently from the inlet air volume and the particle density in the fluidized bed.

3.3. Drying of verum granule under real process conditions

Since MRT is an indirect measuring method, calibration against a suitable reference method is essential. In the primary experiments with placebo granules, calibration was performed against LOD/IR and as mentioned before, a good correlation between MRT and LOD/IR was achieved. Due to the fact that an indirect measuring method can be only as good as the established reference method, the Karl Fischer titration was chosen as an additional reference method for the investigations into the drying of verum granules. Both reference methods have limitations. It is questionable whether LOD/IR is able to detect all physically bound water in samples of different nature. The results from Karl Fischer titration may be influenced by the chemical properties of the drug molecule and the excipients. It is assumed in general that Karl Fischer titration is more accurate for the determination of water in granules than the LOD/IR. By using two independent reference methods for calibration, comprehensive data should be obtained regarding the accuracy of MRT for moisture measurements. At given time points samples were withdrawn and the water content was analyzed using Karl Fischer titration. The obtained results (not presented in this paper) were used to recalibrate the sensor by providing product-specific correction factors using the supplied sensor software. The obtained calibration factor was used in all subsequent experiments with verum granules.

The end-point for the drying of API containing granules was set to 3.8% as it is fixed in the product specification of the licensed drug product. In Fig. 9 the specified moisture limit is indicated by the dashed line. In a first experiment, the drying process was discontinuously monitored by LOD/IR as previously done in the production process, but additionally controlled by continuous in-line MRT. Fig. 9 displays the moisture values determined off-line by LOD/IR and in-line by MRT. At the beginning of the drying process of the first granule batch the water content was 5.7%. The process had to be stopped for six times until the granules met the specified residual water content measured by LOD/IR (Fig. 9). The moisture track of the MRT sensor displays these interruptions of the process as well, since the granules were not fluidized through the sensitive area of the sensor. Therefore, a plateau was formed by these interruptions. Overall, after a process time of approximately 1 h the water content of the granules met the requirements and the drying process was finished.

In a second experiment, the drying process was not interrupted for sample withdrawal and external time-consuming analysis. The process was stopped at the specified end-point of the residual water content, now only controlled by MRT (Fig. 9). At the beginning of the drying process the moisture of the second granule batch was about 6%. After fifteen minutes the measured water content met the requirements by 3.6%. The water residuals in the finished granules were measured by LOD/IR and Karl Fischer titration afterwards, The results were in very good agreement with the MRT signals. By comparing the off-line and the in-line monitoring of the granule water content of both granule batches a time-saving of about 45 min was achieved which is 75% of the total process time for drying. Furthermore, it is obvious that the risk of critical changes in the physiochemical properties of the granules can be significantly minimized by using the new MRT sensor. The discontinuous water determination causes an inhomogeneous drying process. The fluidization of the bed is stopped for the external measurements and the granules rest at the bottom of the product container. By contacting the heated wall of the container the granules may dry further, whilst the granules located in the middle of the product container could wet again. This implicates that it is hardly possible to ensure, that the obtained moisture value of the off-line water determination complies with the actual water concentration in the granules. Furthermore, it is difficult to gain insight into the real moisture distribution within a granule batch. Considering these disadvantages it becomes obvious, that an in-line determination of the granule moisture using the new MRT sensor is associated with formidable benefits for the granulation process and the quality of the final products.

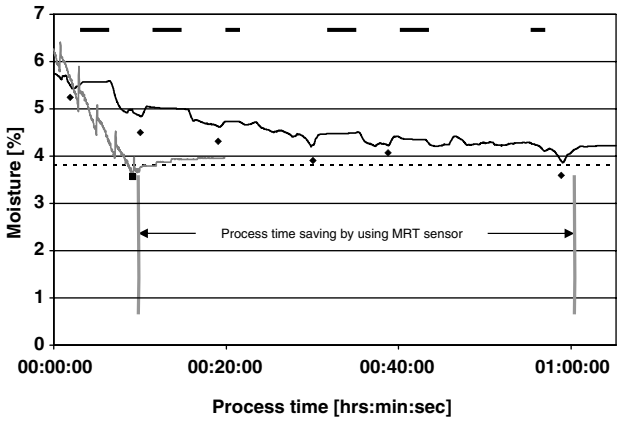

Fig. 9. Drying of verum granules in WSG 60 and the reduction of process time by using MRT for end-point determination. (- - -) Specified moisture of the finished granules. (♦) Loss on drying by infrared light (LOD/IR) within the discontinuous process. (▬) Microwave resonance signal during the discontinuous process. (—) Microwave resonance sensor during the continuous monitored process. (■) Loss on drying by infrared light (LOD/IR) after the continuous process. (- -) Time periods of process interruptions for sample withdrawal and external analysis.

During granulation in fluidized-bed dryer WSG 60 a surprising phenomenon was found. At regular intervals maxima in the granule moisture track were observed, which exactly correlated with the time points of the period-

ically induced vibration of the fine particle filters in the Glatt dryer for cleaning purposes. Most recently, similar observations were reported by Schmidt-Lehr et al. within their on-line measurement of particle sizes using a laser probe in fluidized-bed granulation [16]. Obviously, the vibration of the fine particle filters has an influence on the granulation process by continuously detaching fines from the fluidized bed to the filters and discharging them to the bed periodically. Further investigations will have to clarify the influence of this phenomenon on the moisture distribution within the fluidized bed and the quality of the finished products.

4. Conclusion

A new microwave resonance sensor, appropriate for use in pharmaceutical fluidized-bed processes, was successfully developed and established. By implementing this technique in two different fluidized-bed dryers, the in-line granule moisture measurement using MRT has been proven to be precise and accurate. The technology enables the continuous monitoring of drying processes and the process steering to specified end-point conditions.

The MRT moisture values feature good correlations with the reference methods LOD/IR and Karl Fischer titration. Furthermore, a considerable time-saving of the drying process can be achieved by the in-line moisture determination. The continuous in-line granule moisture determination is associated with a reduction of different risks, caused by process interruptions for sample withdrawal and external moisture determination and inhomogeneous moisture distribution in the apparatus. Hence, the intention of the PAT approach is fully achieved in the case of drying particles from aqueous granulation processes.

Further investigations will focus on the in-line moisture measurement of granules containing large fractions of hydrates. Further, the sensor will be tested for monitoring the complete granulation process and other processes in fluidized-bed apparatuses such as non-aqueous granulation and film coating.

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