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Design, development and method validation of a novel multi-resonance microwave sensor for moisture measurement

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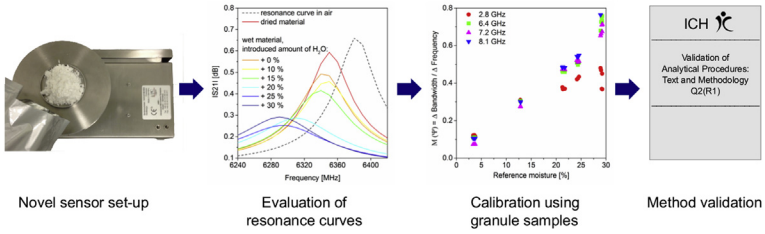
HIGHLIGHTS

- Development of a novel multi-resonance microwave sensor system.
- Explanation of material- and resonance frequency related restrictions of first generation sensor systems.
- Development of a quantitative MLR model for moisture content determination.
- Expansion of measurement range up to 19.6%.
- Method validation according to ICH Q2(R1) for off-line and at-line use.

GRAPHICAL ABSTRACT



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ABSTRACT

Microwave sensor systems using resonance technology at a single resonance in the range of 2–3 GHz have been shown to be a rapid and reliable tool for moisture determination in solid materials including pharmaceutical granules. So far, their application is limited to lower moisture ranges or limitations above certain moisture contents had to be accepted. Aim of the present study was to develop a novel multi-resonance sensor system in order to expand the measurement range. Therefore, a novel sensor using additional resonances over a wide frequency band was designed and used to investigate inherent limitations of first generation sensor systems and material-related limits. Using granule samples with different moisture contents, an experimental protocol for calibration and validation of the method was established. Pursuant to this protocol, a multiple linear regression (MLR) prediction model built by correlating microwave moisture values to the moisture determined by Karl Fischer titration was chosen and rated using conventional criteria such as coefficient of determination (R^2) and root mean square error of calibration (RMSEC). Using different operators, different analysis dates and different ambient conditions the method was fully validated following the guidance of ICH Q2(R1).

The study clearly showed explanations for measurement uncertainties of first generation sensor systems which confirmed the approach to overcome these by using additional resonances. The established prediction model could be validated in the range of 7.6–19.6%, demonstrating its fit for its future purpose, the moisture content determination during wet granulations.

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1. Introduction

Microwave resonance technology (MRT) sensor systems have been used for decades for real-time moisture sensing in many industrial areas. They ensure fast and reliable measurements e.g. in agricultural [1,2], food [3–5] and wood processing industries [6].

First inline applications in pharmaceutical processes were successfully introduced in 2008 by our group [7]. Within further studies, limitations above moisture contents of 7.5% became obvious [8,9]. The technology did not yet find its way in pharmaceutical applications to the same extent as the near-infrared (NIR) sensor systems [10–12].

Nevertheless, the general interest of the pharmaceutical sector in microwave moisture sensing has not been declining. MRT sensor systems were repeatedly deployed in fluidized bed granulation [13–15], high shear granulation [16,17] and roller compaction processes [18,19], where they convinced with highly accurate determinations and reduced calibration efforts compared to near-infrared (NIR) sensor systems. While NIR sensor systems can only measure at the surface of a material under test (penetration depths in the μm-range), microwaves penetrate orders of magnitude deeper and measure volumes, thereby yielding more representative results.

However, in all published pharmaceutical applications so far, measurement ranges have been limited to maximum 14% of relative moisture [16], while most others complained about non-linear behavior of measured parameters already at 7% moisture content [20]. Such a narrow range is perfectly reasonable for application in roller compaction but especially in wet granulation, optimal sensor performance at different moisture levels has to be ensured.

First explanations of these limitations and an approach to overcome them were published in 2010 [21]. The presented sensor system employs multiple resonances at various frequencies and determines relative moisture levels of up to 50% unambiguously. It was employed for moisture content measurement of wood chips. The same approach was adopted for measurements on pharmaceutical materials recently employing a dual-frequency resonator [22]. The benefit of an additional, higher resonance frequency was observed and reported for powders of varying moisture. Nevertheless, data required sectional interpretation resulting in scattering moisture predictions around the threshold. Material and resonant frequency dependent backgrounds were taken up but the studies were limited on microwave moisture values (Ψ). More detailed investigations on the level of resonance frequencies were not conducted.

The tasks of another novel microwave sensor, which similarly employs multiple resonance frequencies, were limited to lower moisture levels not exceeding a maximum of 6.5% [19,20].

Therefore, investigations on multi-resonance microwave sensor systems need to be extended. Changes of the resonance frequencies caused by different excipients at varying moisture levels need to be investigated in order to gain a better understanding of the complex interactions. Thus, the system's behavior at different moisture levels, or – considering later transfer to real-time monitoring – during different process steps, can be better predicted.

Enhanced process understanding gained by use of analytical sensor systems is one of the main objectives of the United States Food and Drug Administration's (FDA) process analytical technology (PAT) initiative [23]. Moisture content determination is a key element of PAT during pharmaceutical processes. While monographs on near-infrared spectroscopy in European [24] and United States Pharmacopeia [25] suggesting performance tests and a specific (draft) guidance for NIR method development and validation [26] are available, no such documents exist for microwave moisture sensing.

Nevertheless, for future inline applications of the MRT sensor in the pharmaceutical world, a thoroughly developed and validated method is crucial, especially as microwave sensors must be calibrated separately for different materials. Therefore, method performance requirements stated in ICH guideline Q2(R1) "Validation of Analytical Procedures" [27], the only available guidance document without explicit application and with multi-purpose worldwide acceptance, were systematically studied.

The aim of the present study was to explore, understand and to overcome material and resonance mode related restrictions of conventional MRT sensor systems. Therefore, a novel multi-resonance MRT system, particularly suited for measurements up to the high GHz range, was constructed. Advantages of a multi-resonance system could be anticipated. The final aim was to develop a model being able to determine the moisture content of pharmaceutical granules even beyond former limits and to fully validate the method taking into account the ICH Q2(R1) specifications. Thereby the suitability of model and sensor systems for future inline moisture monitoring in fluidized bed granulations should be investigated.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (MCC) (Avicel® PH 101, FMC Biopolymer, Philadelphia, USA) and partially pregelatinized maize starch (Starch 1500®, Colorcon, Harleysville, USA) were used for investigations of starting materials.

For method development and validation, granules consisting of 60:40 mixtures of both prepared with an aqueous solution of povidone (Kollidon® 30, BASF, Ludwigshafen, Germany) were used.

2.2. Methods

2.2.1. Microwave resonance technology

Moisture determination by microwave resonance technology (MRT) is based on the interaction of water molecules with the electromagnetic stray field on the MRT sensor's surface. The extent of interaction and resulting modification through the material is measured.

The field interaction with a dielectric material compared to the field in vacuum is described by the complex relative permittivity

$$\varepsilon_r = \varepsilon' - j\,\varepsilon'' \quad (1)$$

where ε' is the real and ε'' the imaginary part (j is the imaginary unit). The real part ε' (also called dielectric constant) reflects the polarizability and describes the ability of a material to store electrical energy. By loading the resonator with a dielectric an increase of stored electrical energy lowers the resonance frequency (f_0 unloaded, f_1 loaded) of the associated resonance mode, Fig. 1. The imaginary part ε'' (the loss-factor) describes the dissipation of electrical energy in form of heat, which leads to an attenuation and relative widening of the resonance curve (resonance bandwidth B_0 unloaded, B_1 loaded, measured e.g. at the half power bandwidth).

While typical dry pharmaceutical excipients have a relatively low permittivity at ambient temperatures and in the frequency band between 2 and 9 GHz ($\varepsilon' < 3$ for MCC and maize starch [16,28]), the permittivity of water ranges from 80 to 65 at 20 °C in the same frequency band [1]. Thus, the interaction of an electromagnetic field with a moist material is significantly depending on the amount of water.

Especially in granular materials, the described changes in frequency and bandwidth are not only dependent on material's