

Multi-resonance Microwave Sensors for Moisture Monitoring in Fluid-bed Processes

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Johanna Peters

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aus dem Institut für Pharmazeutische Technologie und Biopharmazie
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Berichterstatter:

1. Prof. Dr. Jörg Breitzkreutz
2. Prof. Dr. Dr. h. c. Peter Kleinebudde

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List of abbreviations

AE	acoustic emission
API	active pharmaceutical ingredient
ASTM	American Society for Testing and Materials
BCD	Bohle Continuous Dryer
BFS	Bohle Fluid Bed System
CFR	Code of Federal Regulations
CPP	critical process parameter
CQA	Critical Quality Attribute
ΔB	increase of bandwidth
Δf	resonance frequency decrease
ΔH_{vap}	latent heat of vaporization
DoE	design of experiments
ECT	electrical capacitance tomography
EMA	European Medicines Agency
ϵ'	dielectric constant
ϵ''	dielectric loss
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
GPCG	Glatt Powder Coater Granulator
HEPA	high efficiency particulate air
HPC	hydroxypropylcellulose
HPMC	hydroxypropylmethylcellulose (Hypromellose)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPC	in-process control
IR	infrared
KF	Karl Fischer titration
LOD	loss on drying
LOD/IR	loss on drying by infrared light
M (Ψ)	microwave moisture value
MCC	microcrystalline cellulose
MLR	multiple linear regression
MRT	microwave resonance technology

List of abbreviations

MVDA	multivariate data analysis
n	number of measurements
NIR	near-infrared
NMR	nuclear magnetic resonance
PAT	process analytical technologies
PCA	principal component analysis
PCR	principal component regression
Ph. Eur.	European Pharmacopoeia
PLS	partial least squares regression
PVP	polyvinylpyrrolidone (povidone)
QbD	quality by design
RF	resonance frequency
R ²	coefficient of determination
RMSEC	root mean square error of calibration
RMSEP	root mean square error of prediction
RN	indication of an organic base
RSD	relative standard deviation
SNV	standard normal variate
USP	United States Pharmacopeia
VBA	Visual Basic for Applications

1. Introduction

1.1. Fluid-bed granulation

1.1.1. Introduction to the process

Fluid-bed granulation is a process of size enlargement that forms fine particles to larger agglomerates called granules. It employs a liquid binder that is sprayed onto the powder particles in a fluidized state to promote their growth. After granulation, the primary particles can still be distinguished within the resulting agglomerates [1]. It is often used as an (intermediate) process in different industries such as agriculture, mineral processing, pharmaceutical production, foodstuff and specialty chemicals [2]. Typical aims of granulation are: to form uniform granules with improved product homogeneity, to improve flow of particulates, to avoid segregation, to enable dust-free handling, to impact compaction properties and, particularly in the case of pharmaceutical applications, to adjust the strength of resulting compacts as well as dependent disintegration and dissolution. The latter, however, is linked to the presence of an active pharmaceutical ingredient (API) within the granules, which is common in drug products or their intermediates and is a reason to prefer fluid-bed granulation over other techniques. Especially in fluid-bed granulation, resulting material can exhibit high porosity. The loose structure then maximizes the available specific surface and promotes the breakdown of granules following contact with aqueous media, e.g., in the human gastrointestinal tract, resulting in early and full release of the API.

A fluid-bed granulation can typically be divided into the sequential process phases (pre-)heating, spraying and drying, which are all conducted using the same equipment. The heating process is associated with mixing of the particles, which are set in motion by air, and is conducted until a pre-defined temperature or process duration is reached. As fluid-bed granulation belongs to the category of wet granulation technologies, a liquid binder is subsequently sprayed onto the mixed and fluidized powder bed. The powder particles are bound together by liquid bridges that solidify by crystallization of dissolved components or hardening of the binder upon evaporation of the liquid during the drying phase [3].

The underlying phenomena of wet granulation on microscopic level have been examined by Ennis [4], and can be described as a combination of a) wetting, nucleation and binder distribution, b) consolidation and growth and c) attrition and breakage (Figure 1).

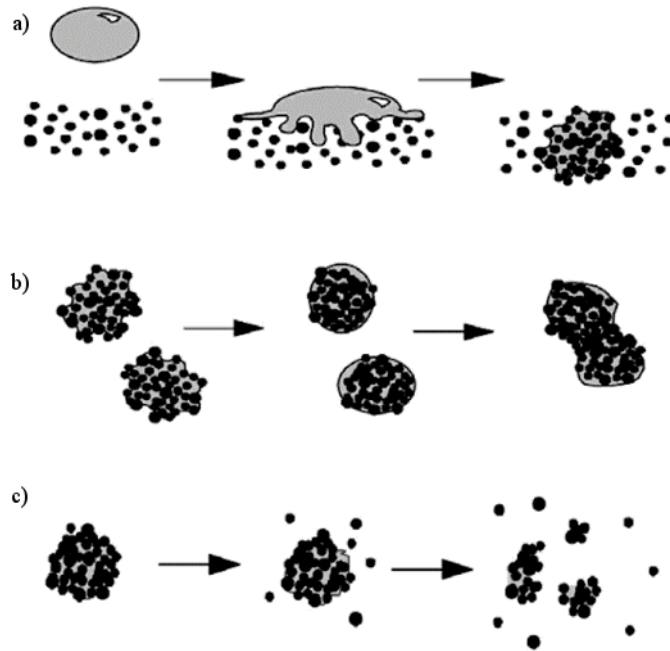


Figure 1: Schematic figure of the granulation process: a) wetting, nucleation and binder distribution, b) consolidation and growth and c) attrition and breakage (modified from [2] and [5]).

Within this work, the rate processes as described by Iveson [2] as well as Litster and Ennis [5] are considered. More recently, Ennis classified the same processes into four key mechanisms by separating consolidation from coalescence and growth [1].

First, liquid binder solution is sprayed onto the dry powder bed and within the spray zone droplets are formed, which moisten and imbibe into the powder and form single granule nuclei upon contact with particles. Usually, the resulting nuclei size distribution correlates with the size of dispersed binder droplets within the spraying solution. If wetting or imbibition into the powder particles progresses inefficiently and slowly (e.g., due to a high contact angle or poor flow characteristics), this results in a broad distribution of particle sizes, leading to poor final granule properties, if not corrected, e.g., by mechanical mixing.

Upon collision with other granules or fine powdered material, coalescence resp. layering may take place, which promotes granule growth. In general, successful coalescence requires the absorption of the impact energy during collision to prevent from rebound and formation of strong bonds upon contact. Whether or not the colliding material sticks together depends on various factors, such as the intensity of agitation within the powder bed, the availability of liquid binder at the interface and the deformation behavior of colliding particles. During consolidation, entrapped air or even liquid binder are squeezed out to the surface of the resulting agglomerates. Porosity and size reduction of the granule takes place. This critically influences the strength of the resulting granules: those with a

higher porosity are weaker and more friable during further processing, handling or storage.

The third-rate process describes degradation procedures: one is the breakage of wet granules into several fragments, which reduces the size of the final granules, and the other is the attrition or fracture of dried granules. The former can be beneficial in limiting the upper granule size, and the latter is undesired, since it results in dusty fines, which are the opposite of the targeted uniform agglomerates.

All these processes occur simultaneously, and their combination controls the final granule attributes. Depending on the raw materials, employed equipment and process routes, different processes are dominant and the resulting granule properties differ accordingly. In the case of fluid-bed granulation, e.g. the wetting process is more pronounced, and consolidation is less prominent as compared with high-shear mixers, where higher mechanical forces are applied [1]. While breakage is also associated with high intensity processes and is used to limit the resulting granule size, attrition and fracture of granules play a role during fluid-bed granulation. This can cause wider particle size distributions [6] and undesired fines due to collision with other granules and bed walls, since the particles encounter high air velocities [5], if not properly controlled. In comparison with high-shear granulation and dry granulation, the granule size distribution resulting from fluidized bed processes is rather narrow, and the reduced mechanical stress faced during production results in higher porosity, which can be associated with superior compactibility [7, 8].

1.1.2. Introduction to the equipment

The application of fluid-bed processes for pharmaceutical production was first reported by Wurster [9, 10]. While these first reports examined the film-coating of tablet cores and particles, only minor equipment modifications were necessary to conduct granulation processes in the same equipment [11–13]. In comparison with alternative multi-stage wet granulation processes, fluid-bed granulation has the main advantage that initial mixing of components, spraying of liquid binder and subsequent drying can all be conducted using the same equipment. It requires fewer handling steps, reduces time and space requirements [3], removes the need for further equipment (e.g. for an additional dryer) and at the same time facilitates production under GMP conditions. While operating costs for air handling may be high, very good heat and mass transfer, resulting in reduced operating times and small losses, outweigh this disadvantage [5]. Although equipment manufacturers continue to produce novel, advanced fluid-bed apparatuses, the basic setup has remained relatively unchanged over the years.

Figure 2 shows the basic configuration of different types of fluid-bed granulators for granulation (top-spray, bottom-spray and bottom-tangential-spray) by exemplary schematic representation of the key elements.

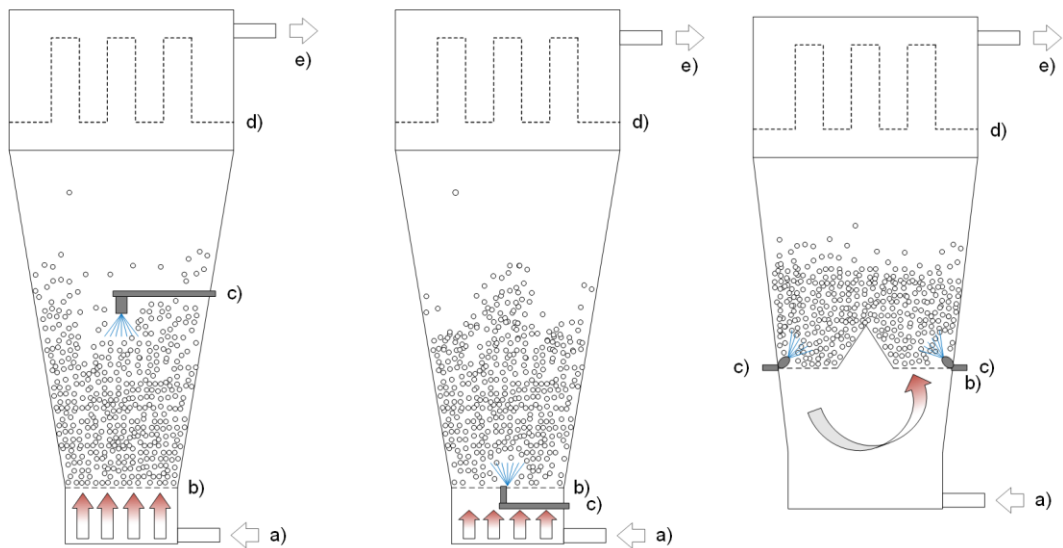


Figure 2: Different set-ups of fluid-bed granulators (from left to right): top-spray, bottom-spray and bottom-tangential-spray setup. a) inlet air (filtered, heated), b) air distributor plate, c) spraying nozzle (with lance), d) product filter, e) outlet air (filtered).

In general, ambient or pre-conditioned air, which is used as the fluidizing medium, passes an air handling unit, where it is filtered and heated. Depending on local conditions and the sensitivity of the product, preconditioning of the air can be realized by the installation of a (de)humidifier. The heated and filtered inlet air (a) enters the fluid-bed through an air distributor plate (b). It forms the lower boundary of the product chamber and also holds the particle bed during loading and discharge. Once the velocity of the air causes a drag force that is equal to the apparent weight of the particles within the bed, they are suspended by the air stream and move upwards chaotically until the conical expansion of the product chamber causes a reduction in air velocity and the particles fall back into the fluidized bed by gravity. Once the particles are adequately mixed, binder solution is added through a spray nozzle. Within the fluidized bed, the particles come into contact with liquid binder, which can be sprayed by single or multiple nozzles (c). Depending on the setup, nozzles are located above (top-spray), below (bottom-spray) or at the side of the fluidized bed (tangential-spray) and feature a single or multiple heads. Liquid binder is typically fed by a peristaltic pump and atomized by pressurized air. After spraying, the resulting granules are kept in the fluidized state to allow drying of the product in the hot air stream. During this process, product filters (d) consisting of socks made from filter cloths or stainless-steel mesh filters retain fine particles as the air flows upwards through

the system and return them to the process upon filter-cleaning by mechanical shakers or jet-pulses of compressed air. The outlet air (e) then escapes through an exhaust air duct system equipped with high efficiency particulate air (HEPA) filters. The airflow necessary for operation is created by a suction ventilator positioned after the filters. Other built-in components, which are not displayed within Figure 2, but are discussed within this work, are sampling probes and sight glasses, which are usually located in the expansion zone of the product bowl.

1.1.3. Equipment types and configurations

In the most frequently used set-up, the top-spray granulation [14], the spray nozzle is installed in the upper part of the product chamber, above or slightly within the fluid-bed, and the binder is sprayed on top of the particles. In comparison with other setups, this processing option tends to spray-drying, increasing the risk of caking on spray nozzles [15], which requires careful formulation and process design. Within this work, this set-up was employed using two comparable lab-scale apparatuses (GPCG1 and GPCG 1.1, Glatt, Binzen, Germany).

In bottom-spray processing, the spray nozzle is located at the center of the air distribution plate, at the bottom of the product chamber, and liquid binder is sprayed concurrently to the air flow. The setup reduces the tendency towards spray drying, since droplets directly contact the fluidized particles and the high impact of the bed mass on the spray nozzle(s) minimizes the risk of cake formation. Resulting granules can be of higher bulk density than those yielded by top-spray processing [15]. Bottom-spray fluid-bed devices are mainly employed in coating processes, and in such cases often feature an additional cylindrical partition (called the “Wurster column”) in the center of the product chamber and an air distribution plate with larger perforations below this [16]. Consequently, higher velocities within the partition are enabled, resulting in a controlled, fountain-like movement through the partition, which is associated with uniform particle residence times in the spray zone and hence a higher coating homogeneity. Due to this directed circulation, the Wurster-based process does not contain a fluidized bed in the traditional sense [17].

A special setup suited to granulation as well as particle coating is bottom-tangential-spray processing. Within this work, this technique was employed using the pilot-scale Bohle Fluid Bed System (BFS 30, L.B. Bohle, Ennigerloh, Germany), which features a product vessel with a specially slotted air distribution plate and a central cone [18]. The process

air enters through the slots and a rotational airflow creates a rotational movement of fluidized particles, resulting in additional blending of particles during processing. The central cone prevents the formation of a potential dead zone in the enclosed area and supports complete fluidization. Spraying nozzles are located at the bottom and spray tangentially into the particle bed. The system thereby ensures thorough mixing and combines the benefits of the bottom-spray setup with the advantage that no additional inserts or setup changes depending on the conducted process are needed.

Other, well-established devices designed to combine the benefits of mixing and fluidized beds are rotary fluid-beds, which were developed for the coating of granular material [19] but are also suited to granulation [20]. Here, the rotational upward movement of particles is created by a rotating disk, which replaces the air distribution plate, and the vertical movement caused by the inlet air, which penetrates through a gap around the disk. The liquid binder is sprayed tangentially from nozzles located at the bottom of the product bowl. This equipment produces more spherical and denser granules as compared with top-spray processes.

In addition to the Bohle Fluid Bed System used in this study, several fluid-bed devices with intensive and directed particle movement have been introduced by equipment manufacturers in recent decades. Prominent examples that can be used for granulation processes are Hüttlin's Kugelcoater [21] which operates using the bottom-spray technique with tangentially spraying nozzles and Innojet's VENTILUS® system. The former differs from the previously described bottom-tangential-spray setup regarding the introduction of process air (in earlier models through a central, stationary pipe [22], in later models, air is introduced from the bottom to the top [23]) and redirected to tangential movement below the air distributor plate. The latter features a cylindrical product chamber and operates with only one radially spraying nozzle placed in the middle of the highest of several circular overlapping baffle plates which allow introduction of process air through the slots in between [24, 25]. This results in a radial tangential upward movement of particles. In all the above-mentioned systems, particles are moved by a controlled air flow bed, but no fluidized bed exists in a traditional sense.

1.1.4. Current developments

Over the last two decades, the pharmaceutical industry has exerted increasing effort to understand the scientific and engineering principles involved in the employed manufacturing processes and to identify the variables, which affect product quality. This

development was encouraged by the U.S. Food and Drug Administration's (US FDA) process analytical technology (PAT) guidance [26] and the International Council of Harmonization's (ICH) quality-by-design (QbD) paradigm [27–29]. The basic principle behind QbD is that quality should be built into pharmaceutical products with an understanding of the raw materials and unit operations by which they are developed and manufactured. Additionally, the risks involved in the production of drug products should be identified and risk mitigation strategies should be elaborated and applied. Consistent with this principle, it was recommended to implement PAT tools in order to increase the process knowledge by measuring key variables, facilitate identification of risks and minimize them at the same time. In most cases, the successful implementation of PAT tools might be time and cost intensive if modifications and adaptations of the equipment are required but does not demand the development of new equipment designs.

More recently, regulatory authorities encouraged to adapt from traditional batch processes to continuous manufacturing of solid oral dosage forms. In the just published draft guidance on quality considerations for continuous manufacturing, the US FDA defined continuous manufacturing as an integrated process that consists of a series of two or more unit operations, in which the input materials are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system [30].

Expected advantages of continuous processes are the facilitation of scale-up, reduced time to market and cost savings derived from a reduced environmental foot-print and improved process efficiency [31–33]. Unlike inherently continuous processes, such as extrusion or tableting, wet granulation has always been a bottleneck in the implementation of continuous pharmaceutical manufacturing [34]. For years, high-volume products in the chemical, dairy and food industries have been agglomerated or dried using horizontally operating continuous fluidized bed granulators, with throughputs of up to several tons per hour. Although horizontally moving fluid-beds fulfilling GMP requirements have been designed, their applicability to the pharmaceutical sector is limited due to long residence times and high throughput rates but restricted drug substance availability during development [35]. Therefore, manufacturers have focused on other techniques to offer continuous wet granulation of particles in integrated from-powder-to-tablet lines. Currently, granulation with twin-screw extruders is considered the most promising technique. By adaptation to an appropriate screw-configuration and removal of the die plate, a modified extruder can conduct continuous granulation at a flexible output capacity [36, 37]. Commercially available equipment combines this

technique with fluid-bed drying (e.g. QbCon® by L.B. Bohle, MODCOS system by Glatt [38]). The most prominent example is GEA Pharma Systems' modular ConsiGma™ system featuring a drying module based on a conventional fluid-bed segmented into six sub-units, which is available for the production of approx. 25, 50 and 100 kg per hour [39] or as a small-scale development unit [40]. Continuously produced granules are divided into sub-batches of e.g., 1.5 kg using the ConsiGma™-25 and alternately filled into one of the six cells of the horizontally divided product bowl. Once the granules are sufficiently dried, the material is discharged and the granule properties are assessed, while the dryer's sub-unit is filled for a new cycle [35]. Within this thesis, experiments were conducted on a similarly operating semi-continuous fluid-bed drying unit, the Bohle Continuous Dryer (BCD) 25. It was an integrated part of Bohle's flexible continuous manufacturing line QbCon® 25, and serves to dry granules produced by twin-screw granulation, which are alternately transferred into a series of four single drying chambers. In the meantime, the drying unit of said continuous processing line is optimized based on good results of the small-scale development unit, QbCon® 1. Within this unit, an integrated, horizontally operating fluid-bed, which is excited by vibration, moves the material plug flow with a narrow residence time distribution from feed zone to discharge, realizing truly continuous drying [41].

Since continuous wet granulation and drying for commercial manufacturing are limited to Vertex's drug products ORKAMBI® and SYMDEKO® resp. SYMKEVI® (the other approved continuously produced drug products, Janssen's PREZISTA® and Eli Lilly's VERZENIO® resp. VERZENIOS® are manufactured by direct compression), and other vendors are still constructing integrated drying equipment based on alternative approaches (e.g., spiral drying in Freund Vector's Granuformer®), truly continuous wet granulation and drying units will certainly gain momentum in the near future.

1.1.5. Moisture as a Critical Quality Attribute

Granules yielded from wet granulation are always prone to solvents. Needless to say, the level of moisture introduced during aqueous processing steps, such as wet granulation, could result in processing-induced phase transitions (e.g., the formation of hydrates) [42], but residual amounts that remain after drying also influence the material. Irrespective of whether an organic solvent is used or aqueous processing takes place, residual amounts of the process material must be controlled. While the ICH has adopted a guideline specifying limits for organic solvents that may remain in the medicinal products based on toxicological assessment [43], formulators are relatively free to adjust the residual water content in drug products. Nevertheless, an appropriately specified moisture range is

crucial. Elevated or reduced residual moisture can lead to obstacles during downstream processing such as poor flowability, de-mixing tendencies and deteriorated tableting properties [44], which can alter the physical properties of the final dosage form (e.g. breaking strength, friability, disintegration time) [45] and can negatively influence drug product stability (e.g. by hydrolysis of the API) [46].

Among the interactions between water and solid materials, crystalline solids must be distinguished from amorphous solids. In crystalline solids, water can be adsorbed onto the particle surface, may form crystal hydrates, and show deliquescence or capillary condensation [47]. While the amount of water introduced by surface adsorption is limited, amorphous materials have a high capacity for water vapor sorption, and their bulk properties can be altered accordingly [42], resulting in higher criticality of the finished product. In particular, starches, celluloses and their derivatives are widespread in pharmaceutical dosage forms and are known to take up and retain significant amounts of moisture [48, 49]. From this group, the partly amorphous materials, microcrystalline cellulose (MCC) and (pregelatinized) maize starch, were studied within this thesis. In starches, the introduction of water results in the hydration of amylose and, depending on the temperature, in the gelling of amylopectin. Due to the close packing and high degree of order, MCC's crystalline regions (accounting for approx. 63 % of the material [50]) do not participate in the uptake of water [48], while water sorption occurs uniformly throughout the solid fraction of starches. In both materials, the present water can be classified as "bound" or "solvent-like" [51]. Since the latter can be transferred from the excipient to other ingredients (e.g., the drug substance) by vapor phase or capillarity [48], this portion is more reactive, tends to redistribute and needs to be monitored carefully. Their small size and high polarity allow water molecules to penetrate into the amorphous polymer structure and increase its free volume, thereby acting as a plasticizer. Depending on the extent, this causes a transition from glassy to rubbery state and increases the mobility of molecules or molecule segments within the material, alters viscoelastic properties and hence critically influences processing properties of the solid, such as direct compaction behavior [51].

In summary, moisture content of granules affects processing, purity, drug release and stability, and is a perfect example of a Critical Quality Attribute (CQA) as defined by the ICH's Q8(R2) guideline "Pharmaceutical Development" as "a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality" [27].

1.1.6. Critical Process Parameters

Long before the aforementioned ICH Q8(R2) guideline “Pharmaceutical Development” underlined the importance of the knowledge of process parameters “whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality” [27] and named them critical process parameters (CPP), those affecting granule attributes in fluid-bed granulation have been evaluated in various studies.

In his first journal article on pharmaceutical fluid-bed granulation in 1960, Wurster reported that low column humidity and water content were related to fines, whereas the granules with the highest moisture content clearly exhibited larger particle sizes [13]. In addition, he described interrelations as the pronounced agglomeration related to lower exhaust air temperatures and stated that control of water content is desired and feasible to enable uncomplicated tableting.

In the 1970s, the effects of spraying rate, atomization pressure, inlet air temperature and nozzle position on the physical attributes of granules were described by Davies and Gloor [52], and further evaluations were published in a series of systematic studies by Schæfer and Wørts. Their first publication focused on the influence of equipment setup and formulation variables [53], and following papers dealt with the influence of formulation and process parameters [6, 54–56]. Key properties of interest were granule growth, size and size distribution. In summary, granule size and growth rate were found to increase proportional to spraying rate, droplet size and concentration of a given binder, and to decrease with higher differences between wet bulb and inlet air temperatures. Granule size distribution was found to decrease with the amount of spraying liquid and to increase with droplet size. Numerous published studies confirmed these relations and have been discussed extensively in various reviews [14, 57–59]. An overview of the most important parameters is given in the Ishikawa diagram (Figure 3). Those parameters that directly influence the moisture content of the fluidized material, and by this influence the quality attributes of the granules, are colored in black; those parameters that do not have a direct influence on the moisture content of the bed, but influence CQAs by other relationships, are colored in grey. Given the multifactorial interplay, interrelationships between parameters are not displayed.

Hereby, it becomes possible to identify that almost all process parameters and environmental parameters, as well as several formulation variables, primarily influence the moisture content of the fluidized bed, which can subsequently impact the quality attributes of the granules.

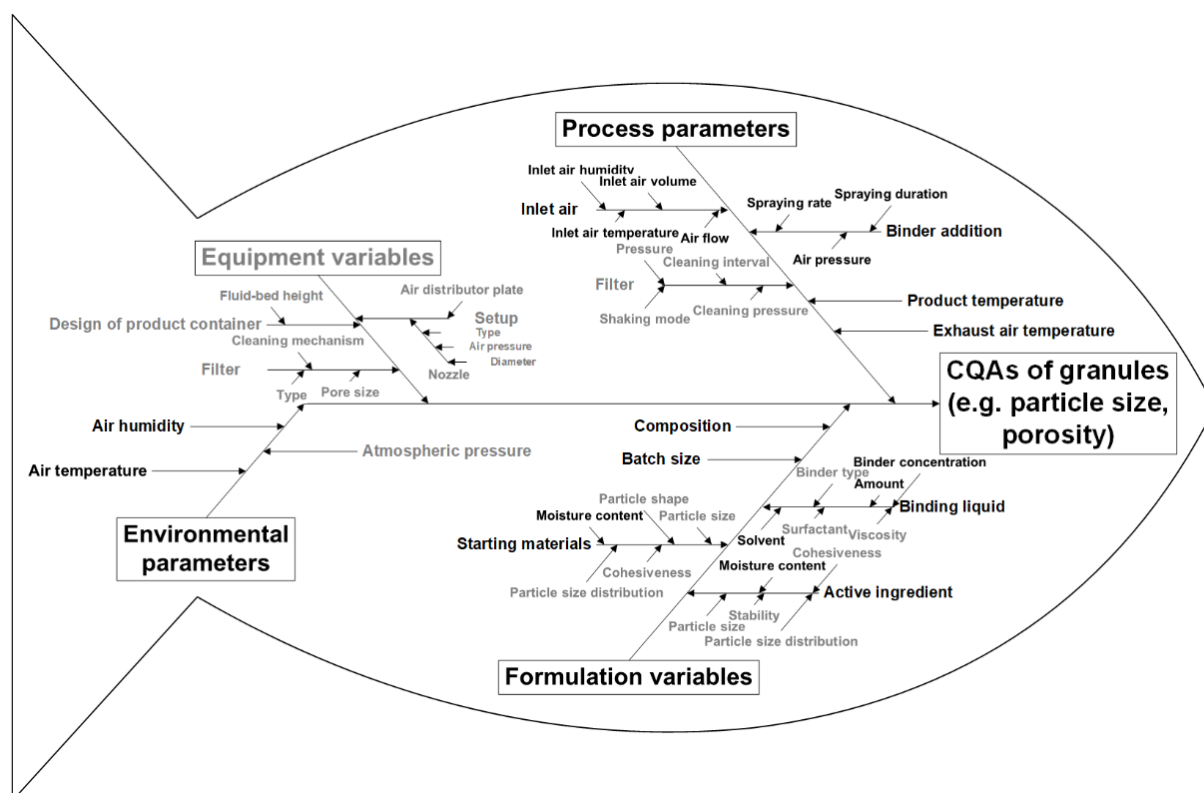


Figure 3: Ishikawa diagram of the parameters in fluid-bed granulation. Those that directly influence the moisture content of the fluidized material are colored black, others are colored grey. Interrelationships between parameters are not displayed for the sake of clarity.

Over recent decades, statistical approaches have been applied to better understand the effect of process parameters and establish optimum settings at different equipment scales [60–66]. Throughout these and following publications, it has been confirmed that fluid-bed moisture content, either resulting from process parameter settings [67, 68] or from variations in inlet air humidity [69, 70], is a crucial factor in determining granule properties. The direct criticality of fluid-bed humidity was discussed by Lipps and Sakr [60]. Rambali et al. [63], found that moisture content, besides droplet size and deformation force by the applied air flow, was the most important parameter. Accordingly, methods to measure and control the moisture content during granulation have been assessed. The first systems were based on infrared sensors [71–73] and numerous publications employing various methods followed. The most frequently employed and reported systems are presented in detail in section 1.2.3.4.

1.2. Moisture content and control in pharmaceutical processes

1.2.1. Definition of moisture content

Moisture content (also referred to as water content) can be defined as the quantity of water in a gaseous, liquid or solid material.

Within this thesis, the terms “moisture content” and “water content” are used synonymously and refer to the relative moisture content of solid materials, which is usually expressed as

$$\Psi [\%] = \frac{m_w}{m_w + m_d} \times 100,$$

where m_w is the mass of water and m_d is the mass of dry material in the measured volume. Moisture content can range from 0 to 100 %.

1.2.2. Water binding types

A classification of moisture content during wet granulation based on early research by Newitt and Conway-Jones is often referred to and applied [74]. In 1958, they classified three states of water content described by the liquid bridges within a granule, namely pendular, funicular and capillary states (Figure 4). In the pendular state, which occurs at low moisture levels, the small quantity of water forms lens-shaped rings around the points of contact of an assembly of spherical model particles. At higher moistures, the rings coalesce, and the funicular state is reached, which is characterized by partially complete pore space filling and a network of liquid with interspersed air. The capillary state is characterized by nearly complete filling of all pores. In this state, the particles are held by capillary suction at the liquid-air interface on the granule surface. To obtain agglomerates in the capillary state, sufficient addition of water or moderate addition of water and mechanical agitation are necessary, which reduces the internal pore space.

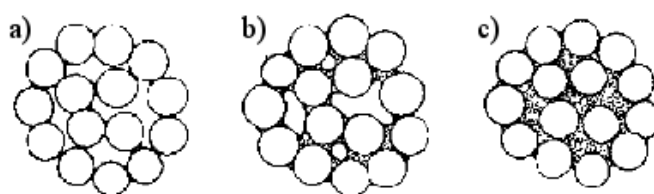


Figure 4: States of water content during granulation: a) pendular, b) funicular, c) capillary state (from [74]).

As this classification gives limited information regarding the origin of the liquid bond and related forces, a more detailed classification is valuable. Water contained in granular material or solids in general can be classified by origin or type. In wet granulation, three different origins exist [75]:

1. Water of constitution is part of the crystal lattice and an essential part of the constitution of a component, usually of the API. It requires high energy to evaporate this water and it should not be evaporated during drying, since the required input of energy would be accompanied by denaturation of the active ingredient.

2. Adsorption water is frequently contained in the inactive ingredients or, even if undesired, in the API. The contained amount depends on the ambient conditions, as it is adsorbed until an equilibrium between vapor pressure inside the granules and the partial pressure of water vapor in the surrounding air is reached. For each material, characteristic adsorption isotherms result based on their hydrophilicity.
3. Added water, on the other hand, is provided by the addition of aqueous or hydro-alcoholic liquid binders.

If classified by type, the mode of water distribution is the decisive factor, and processing behavior (e.g., during drying) can be linked to the bonding type and strength [75, 76], which is also represented in the latent heat of vaporization (ΔH_{vap}) needed to overcome the energy of bonds upon evaporation [77]:

1. Adhesive water or surface water is just weakly bound on interfaces and can be removed easily during drying, since forces are limited to electrostatic or van der Waals forces. Its vapor pressure is equal to that of liquid water enabling easy removal upon drying (ΔH_{vap} : 0 kJ/mol).
2. Capillary water is held by the capillary strength of voids in the material. Depending on the pore size, the vapor pressure of capillary water is also equal to that of liquid water (diameter $> 0.1 \mu\text{m}$, ΔH_{vap} : 0 kJ/mol), resulting in easy removal, or lower (diameter $< 0.1 \mu\text{m}$, ΔH_{vap} : 0–5 kJ/mol), which is connected to further decrease during drying, resulting in hygroscopic behavior.
3. Swelling water is associated with an increase in the volume of the material that it fully penetrates. Its bonds are strong (ΔH_{vap} : 0–20 kJ/mol), resulting in impeded drying.
4. Water of crystallization is chemically bound (ΔH_{vap} : 20–105 kJ/mol) and usually not removed upon fluid-bed drying at moderate temperatures (40–60 °C) in pharmaceutical production.

1.2.3. Moisture measurement

As described in section 1.1.5, moisture is a CQA of granules produced by wet granulation, which determines suitability for downstream processing as well as finished dosage form properties and stability. Consequently, proper moisture control and monitoring in pharmaceutical processes are crucial. Available methods mainly fall into the two categories of direct methods, which can be further subdivided into physical and chemical methods, and indirect methods.

1.2.3.1. Direct measurements

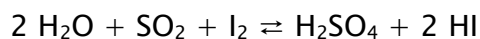
Direct measurements of moisture content should be conducted on representative samples using a known mass or volume of the product and involve the removal of water from the material being tested. This can e.g. be achieved by drying, distillation or extraction, and subsequent quantitation by determining mass or titration. Direct methods are considered as methods of choice leading to reliable results but are commonly material-intensive and time-consuming.

In the pharmaceutical environment, commonly employed and compendial direct measurement methods are loss on drying (LOD) determination and Karl Fischer titration.

Loss on drying is the loss of mass expressed as the mass percentage of the untreated material under test resulting from the loss of water and other volatile matter that can be driven off. Its thermogravimetric determination is conducted on a prescribed quantity of material under specified conditions (Ph. Eur. 2.2.32 [78], USP <731> [79] resp. USP <921> [80]). Drying can be achieved by different procedures, e.g., in an oven, in a desiccator or under high vacuum, on different amounts of sample and for different time periods, until the mass remains constant or for a predefined time interval. It is crucial to define operating conditions in detail to obtain reproducible results and to minimize the evaporation of other volatile substances, which falsify the measurement. While manual weighing of samples prior to and following a period of drying in an oven is time consuming and difficult to perform under pharmaceutical production conditions, moisture analyzers consisting of weighing and heating units are available, which are programmed to weigh, heat and reweigh the sample, followed by calculation and display of the LOD. The heating units of these moisture analyzers are another source of variation as heating and drying of the test material can be achieved by means of infrared radiation (LOD/IR) or by means of microwave radiation. In the case of infrared sources, more (halogen radiator) or less (infrared radiator) effective heat expansion and drying take place. Due to the limited penetration depth of IR radiation, the extent of evaporation is mainly limited to surface water. In the case of microwave drying however, the radiation permeates the material and thus realizes a more complete determination of the contained water [81].

Nevertheless, the partial automation of the procedures, the reduced measurement time (usually 5–15 min) and manageable technical complexity make moisture analyzers a well-established tool for the in-process determination of moisture content and end-point detection during wet granulation.

Karl Fischer titration is a titrimetric method based on the quantitative reaction of water with sulfur dioxide and iodine in the presence of a base with buffering capacity in an anhydrous medium. It was initially described in 1935 by German chemist Karl Fischer and is named after its inventor [82]. His initial report assumed a direct reduction of iodine by sulfur dioxide as an equilibrium reaction that could be conducted in methanol and shifted to the right by the addition of pyridine:



it was found soon after the publication that methanol was involved in the reaction [83]. Further reports in the 1970s [84] and 1980s revealed that pyridine acted simply as a base and could be replaced by imidazole, which was less toxic, reacting more quickly and producing more accurate results [85]. Based on these studies, the following reaction process (with RN as general indication of an organic base) was assumed:



The first reaction step, which already takes place in the reagent, produces the methyl sulfite ion as an oxidizable species from methanol and sulfur dioxide, which is later oxidized according to the second reaction process. In summary, iodine is reduced, and monomethyl sulfite is oxidized to monomethyl sulfate in the presence of water and an organic base. Iodine and water react in a molar ratio of 1:1, and the endpoint corresponds to an excess of iodine.

The titration can either be conducted using volumetric or coulometric endpoint detection. In volumetric analysis, iodine is added in solution, and in coulometric titration, it is generated by electrochemical oxidation within the cell.

Volumetric titration (Ph. Eur. 2.5.12, Method A or B [86], USP <921>, Method Ia or Ib [80]) is preferred in cases where the sample is likely to contain water in larger amounts than in trace amounts. It is performed by the addition of an iodine-containing titrant to the vessel containing the sample and methanol until no further iodine is consumed by the reaction. The endpoint is detected by an excess of iodine associated with a decrease in voltage (if a constant current is maintained) or an increase in current (if a constant voltage is maintained) between the indicator electrodes, which are connected to an electronic source (Ph. Eur. Method A resp. USP method Ia). Alternatively, an excess of iodine can be added to the titration vessel, and a back titration using a water-containing titrant can be conducted (Ph. Eur. Method B resp. USP method Ib).

Coulometric titration (Ph. Eur. 2.5.32 [87], USP <921>, Method Ic [80]) is conducted if the amount of water in the sample is expected in a very low range of less than 10 mg. Iodine

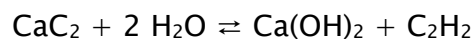
is not added as a titrant but is generated in-situ by anodic oxidation of iodide at a generator electrode within the titration vessel. The generated iodine reacts with the water, resulting in hydrogen ions, in addition to the sulfur dioxide in the reaction cell, until an excess of iodine is generated. At the cathode, the positively loaded hydrogen ions are reduced to gaseous hydrogen. The anode and cathode are usually separated by a diaphragm to prevent iodine molecules from immediate reduction to iodide ions at the cathode instead of reacting with the water. Moreover, the hydrogen gas generated at the cathode forms bubbles and hinders access by iodine. Based on the sensitivity of the method, the absorption of atmospheric moisture must be prevented. Liquid samples can therefore e.g. be injected into the titration vessel through a septum or solid and can be heated in a drying oven under predefined conditions, evaporating the water and can be transferred by nitrogen flow into the titration cell. In all cases, the water content can be calculated as it is directly proportional to the current required for iodine generation during titration.

Using one of the Karl Fischer methods, both physically and chemically bound water is detected. The advantage lies in the high sensitivity of the titration and possible automation by sophisticated instruments. Disadvantages are the more complex technical procedure, toxicity of chemicals, price and limited lifetime of the reagents, the sensitivity to disturbances e.g., by atmospheric moisture or the presence of aldehydes and ketones, which can release water upon reaction with methanol, and the inappropriateness for timely conduction during production processes. Another point for consideration is that the detection of chemically bound water can result in the need for subtraction of the respective share to draw conclusions on behavior during downstream processing related to physically bound water. The necessity of subtraction of the chemically bound water can even lead to further uncertainties, especially if different hydrates are present in the material being tested [81]. Due to the unrivalled sensitivity and availability of systems with high automation, Karl Fischer titration remains the standard method in pharmaceutical quality control and release testing, but not for in-process controls.

Other available direct measurement methods include, but are not limited to, azeotropic distillation and the calcium carbide method [75]. In azeotropic distillation, which is monographed in the US pharmacopoeia (USP <921>, Method II [80]), the material under test is distilled with a water-immiscible organic solvent (e.g., toluene), which forms an azeotropic mixture, and the volume of water is determined from a graduated measuring

tube following phase separation. Accordingly, this method is less suitable to test specimens containing only small quantities of water.

The calcium carbide method is another chemical analysis method that utilizes the fact that calcium carbide produces acetylene in the presence of water:



This assay can be conducted volumetrically or manometrically [75]. Like Karl Fischer titration, this method is destructive, but detects the water of crystallization. Similar destructive direct measurement techniques of limited suitability are gas-liquid chromatography and mass spectrometry.

Reports regarding the application of these latter methods, in general and especially in the pharmaceutical industry, are limited, since their conduction is less user-friendly and automated equipment is not available.

1.2.3.2. Indirect measurements

In indirect moisture measurements, an intermediate variable is measured and mathematically converted into moisture content based on a previously established calibration. Frequently employed methods are based on the interaction of the material with an electromagnetic field in general and often on vibrational spectroscopy.

Electromagnetic moisture measurement techniques are available over a broad range of frequencies, from radio to near-infrared waves. This is associated with the favorable feature that systems are scalable in their sensitivity, and adaption of the electromagnetic field frequency alters the size of interaction volumes [88]. Examples of electromagnetic determination of water content are based on microwave resonance technology (MRT) or nuclear magnetic resonance spectroscopy (NMR). Terahertz radiation also offers a high sensitivity for water but this comes with limitations for the material under test. Merely rather thin samples or samples with limited moisture content can be measured.

Using MRT, the moisture content is determined by the extent of change in an electromagnetic wave caused by (partial) penetration of the material under test. A microwave sensor generates and emits microwaves towards the tested material. Within the material, these microwaves excite water molecules, which alter the propagation of the wave, and this alteration can be detected. The main advantages are that physical contact to the tested material is not required, and therefore sensors do not alter or contaminate the material, that microwaves also penetrate opaque materials and the relative insensitivity of microwave sensors towards environmental constraints like dust or water vapor [89]. Since the higher penetration depth as compared with infrared radiation [90]

and the non-necessity of physical contact between sensor and test specimen qualify microwave sensors as a tool for on-line and in-line applications. They are already utilized in various industrial sectors, as further discussed in section 1.3.

In ^1H -NMR spectroscopy, the detection of water is based on the interaction of ^1H -nuclei with an externally applied electromagnetic field, which possess a strong magnetic moment and are, in the form of the water molecule's hydrogen atoms, in high abundance in wet materials [91]. By introducing a magnetic field, the ^1H -nuclei leave their random orientation and align either with the field or against the field due to their strong magnetic momentum. An excess of those aligned with the field over those in anti-parallel orientation results in a detectable magnetization that is proportional to the overall number of ^1H nuclei in the sample [91] and can therefore be used to quantitate the moisture content. Pulsed NMR is based on the measurement of energy absorption by NMR spectrometers after a coil of circuit generates one or more short pulses of a radio frequency field, usually in the frequency range of 10–40 MHz [92]. It has been reported that by pulsed NMR even a distinction between bound and free water is possible [93]. Although accurate, fast and non-destructive, application of NMR is limited by great financial and technical complexity [81]. The necessary immersion of the sample limited applications for a long time, however, the availability of one-sided access NMR spectrometers now facilitates on-line applications, since they can be applied to the test specimen from one side [91]. Nevertheless, reported applications mainly arise from the area of civil engineering or wood industry. In the pharmaceutical field, measurements based on NMR are limited, and the technique is rather used in polymorph screening during pre-formulation [94] or in pharmaceutical research, e.g., as sophisticated magnetic resonance imaging providing spatial resolution in studies of moisture uptake [95, 96], rather than for moisture determination in quality control testing.

Another moisture measurement method, which is commonly employed in the pharmaceutical field, is vibrational spectroscopy based on mid- as well as near-infrared (NIR) and Raman spectroscopy. While the techniques show differences in several aspects, their basic physical origin is the same: absorption bands in the mid-infrared (wavenumber range $400\text{--}4000\text{ cm}^{-1}$ resp. wavelengths from $2500\text{--}25000\text{ nm}$) or near-infrared (wavenumber range $4000\text{--}12500\text{ cm}^{-1}$ resp. wavelengths from $800\text{--}2500\text{ nm}$) region or in the Raman spectrum can be observed as a consequence of molecular vibrations. Due to different excitation conditions of the different spectroscopic methods, the relationships

between the absorption intensities and the addressed functionalities of the molecules under examination vary significantly. While Raman spectroscopy focuses on vibrations of homonuclear functionalities (e.g. C=C, C-C, S-S), infrared spectroscopy focuses on polar groups (e.g., C=O, C-O, Si-O). In the case of NIR, the focus lies on functionalities such as C-H, N-H and O-H in particular, which exhibit a large mechanical anharmonicity of the vibrating atoms. This explains, why water strongly absorbs in the mid- and near-infrared regions, but hardly detected by Raman spectroscopy [97]. As a result of this and the necessity for sample preparation in the case of mid-infrared spectroscopy, only NIR spectroscopy qualifies as a non-destructive indirect method for water content determination in fluid-bed granulators. Its suitability, especially for continuous moisture monitoring, is evaluated in more detail within section 1.2.3.4.1.

An indirect method, which is claimed to be a chemical-free alternative to Karl Fischer titration, is based on relative humidity sensors. The material under test is heated, and nitrogen, as a dry carrier gas, transfers the thermally evolved gasses to a thermoset polymer capacitor that detects a change in electrical activity [98]. The total moisture release of the sample is then determined by integrating the moisture transmission rate over time. While the pharmaceutical industry continues to follow compendial methods, the described method is commonly employed in the medical devices industry and is specified as an ASTM standard test [99]. Despite of the detection principle based on relative humidity, it should not be confused with measurements of water activity or equilibrium relative humidity, which are conducted e.g. in development and quality control of food materials.

1.2.3.3. Definition of measurement conditions

In the early 2000s, the U.S. FDA formed a new campaign entitled “Pharmaceutical cGMPs for the 21st century”, with the objective of increasing the control and quality of pharmaceutical manufacturing processes. The use of state-of-the-art tools, which have already been proven to optimize manufacturing processes in industrial sectors, was recommended to enable scientific and risk-managed pharmaceutical development and to facilitate and increase process understanding. In addition to data acquisition and management tools, proposed measures also include process analyzers and monitoring tools. Within the framework of the U.S. FDA’s new campaign, a “PAT initiative” was formed, which elaborated the U.S. FDA’s PAT guidance [26]. The term “PAT” stands for “process analytical technology”, and is defined as “a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of

critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality” [26]. This definition was later adopted by ASTM and ICH. In the guidance, some key definitions were introduced to harmonize the understanding of measurement positions and conditions of such tools.

Over the last 15 years, the introduced terms “at-line”, “on-line” and “in-line” [26] have been adopted by pharmaceutical companies to classify measurement conditions of process analyzers, which of course also apply to moisture monitoring tools.

The term “at-line” describes measurements where the sample is removed from the process and analyzed in close proximity; “on-line” means that the tested sample is diverted from the process stream for measurement but may be returned to it; and “in-line” indicates that the property of interest is directly assessed within the process and no sample needs to be withdrawn. An additional term, which was not specified within the guidance but completes the previous classifications, is “off-line”. In this case, the sample preparation, measurement and evaluation are not conducted in close proximity to the process, instead but samples are transferred to another unit, e.g. to a centralized analytical laboratory.

In general, on-line and in-line analyses differ essentially from off-line and at-line analytical technologies. Since the evaluation is conducted directly at the measurement location, variations in the property of interest are immediately detected, whereas in the case of off-line and at-line analyses, sampling, measurement and analysis consume additional time, during which the measured property may already change thereby impeding feedback control.

Real-time release, which means that the quality of the final product is assured based on process data, typically including a valid combination of measured material attributes and process controls [27], demands a quick provision and evaluation of results, and hence for in-line or on-line methods. Although in-line measurements are the quickest option to provide the necessary results, it can be a challenge to prevent fouling of the measurement system, e.g., of a measurement window by a moist mass throughout the process [14].

Despite being more time-consuming, real-time release can also be realized based on at-line measurements, when the obtained quality assurance is at least equivalent to, or better than, laboratory-based testing on collected samples [26].

1.2.3.4. Continuous moisture monitoring techniques in fluid-bed equipment

As mentioned in the previous section, the most favorable moisture monitoring options are those providing reliable real-time moisture control. These methods allow assessment of the conformity to the moisture content range specified in the quality target product profile

and can then contribute accordingly to the real-time release of the drug product or intermediate. While destructive methods, such as Karl Fischer titration or LOD, are inherently discontinuous methods and hence inappropriate, the most often employed method by far to continuously monitor the moisture content in fluid-bed apparatuses is near-infrared spectroscopy.

1.2.3.4.1. Moisture measurement by near-infrared spectroscopy

As outlined previously, the NIR region of the electromagnetic spectrum is commonly defined as the wavelength range of 800–2500 nm, corresponding to the wavenumber range of 4000–12500 cm^{-1} , or more precisely as the spectral region spanning the wavelength range of 780–2526 nm according to the ASTM definition. Absorption bands are related to specific molecules in the analyzed samples. They can be assigned to overtones and combinations of fundamental vibrations of –CH, –NH, –OH and –SH functional groups which are typically broad and 10–100 times weaker than the fundamental mid-infrared absorption bands. While this impedes sensitivity and results in the necessity for chemometric data evaluation, the lower absorption coefficient results in a higher penetration depth and allows direct analysis of strongly absorbing and highly scattering samples in either reflectance or transmittance mode without pre-treatment [100].

The first industrial applications of NIR spectroscopy for quality control were reported in the field of food technology in the 1950ies [101]. However, only limited reports employing and promoting the attractiveness of the NIR region for analytical purposes in the chemical sector arise from this in the following decades [102, 103]. In the 1980s, stand-alone NIR instrumentation became available (previously, the spectral range was just included as an add-on in ultraviolet-visible or mid-infrared spectrometers). In the 1990s, the availability of light-fiber optics coupled with specific probes and chemometric evaluation routines promoted the use in the chemical industry [97].

Moreover, the possibilities of qualitative and quantitative analysis using NIR spectroscopy combined with multivariate data analysis (MVDA) were recognized in the pharmaceutical sector during this time. While the dependence of the NIR signal on physical as well as chemical properties of the tested material enables the determination of various properties such as identity, crystallinity, assay/ content uniformity, particle size and moisture content, only the latter will be in the focus within this thesis.

Since water has five particularly strong absorption maxima in the NIR region (760, 970, 1.190, 1.450 and 1.940 nm), NIR spectroscopy can be effectively used to determine the moisture content of bulk solids [100, 104]. Early quantitative applications of NIR spectroscopy employed filters and were therefore conducted at a relatively small number of wavelengths. These methods involved dissolving of the sample in a solvent with no or little absorption in the spectral region around 1900 nm and quantitatively determining the water content by absorption of the water's OH-group combination band in the transmittance mode [105–107]. The preferred measurement mode has changed over the years, since the main advantage over conventional moisture measurement methods became obvious after increasing availability of NIR spectrometers operating in reflectance mode. In the late 1980s and 1990s, several publications drew attention to the comparably high measurement accuracy combined with less complex or even omittable sample pretreatment and fast analytical responses [108, 109]. In 1992, the U.S. FDA already approved NIR spectroscopy as an alternative method in pharmaceutical quality control [110]. While in most of these applications, spectral interpretation was still conducted based on multiple linear regression (MLR) models comprising a limited number of wavelengths, the availability of computational power at more affordable prices and convenient software packages soon led to the interpretation of whole spectral regions and interpretation by more sophisticated data evaluation methods. Employed methods included principal component regression (PCR) or partial least squares regression (PLS) [111, 112], which enable the simultaneous determination of several components in a sample but avoid issues related to collinearity or noise-related variability in the spectra [113]. The benefit of the reflectance mode could also be fully exploited in these examples, since measurements were conducted directly in the vials or by an inserted fibre optic probe.

The first systematic series of studies on in-line application of NIR spectroscopy in fluid-bed granulators was published by Watano et al. [72, 73, 114]. The authors used it for continuous moisture monitoring in different types of lab-scale fluid-bed granulators. A feedback mechanism controlling further liquid addition based on the results of a fixed-wavelength NIR filter instrument was implemented, and the output of the NIR instrument could be correlated with moisture contents determined on lactose monohydrate, maize starch and hydroxypropylcellulose (HPC) mixtures using the LOD method up to approx. 18%. During the same period, Steffens et al. evaluated the applicability of NIR spectroscopy for moisture measurement. Quantitative PLS models were developed using Karl Fischer titrations as control and provided discontinuous in-line control in high-shear

granulation [115] and continuous on-line control in fluid-bed wet granulations [116]. Since the in-line studies by Frake et al. at 40-kg scale [117], and Rantanen's series of studies conducted on different drug formulations with a four-wavelength NIR spectrometer [118–120], which were later complemented by further insight through full Fourier-transform NIR spectra [121], NIR spectroscopy has gained momentum as a useful tool for continuous moisture measurement in wet granulations and in the pharmaceutical industry in general. Reviews by Blanco [113], Reich [100], Roggo [122] and De Beer [123] provide an overview of the increasing number of pharmaceutical applications realized by more and more sophisticated sensor systems that have become available over the years. These developments have been facilitated by regulatory guidance such as the U.S. FDA's PAT guidance [26] and the ICH's quality-by-design paradigm, which encouraged full understanding of the manufacturing processes throughout the entire life cycle [27–29]. In recent years, the success of NIR spectroscopy as a PAT tool in the pharmaceutical industry and the regulatory endorsement of this method has been further highlighted through an FDA guidance on NIR spectroscopy [124] and the ongoing revision of the United States Pharmacopeia (USP) monograph on near-infrared spectroscopy [125] (which will be divided in monograph <856> on calibration and validation procedures and the general monograph <1119> on theory and practice). Moreover, in the European market, the early implementation of chapter 2.2.40 in the European Pharmacopoeia (Ph. Eur.) [126], a guideline on NIR spectroscopy [127] and the latest adoptions to Ph. Eur. general chapter 2.2.24 on infrared absorption spectrophotometry [128] have led to a higher certainty regarding the health authorities' expectations. The revised chapter recognizes the fact that monochromator instruments are obsolete and describes current Fourier-transform spectrometers. An example of a successfully implemented Fourier-transform NIR method for in-line end-point detection of granulations at commercial scale was reported by Peinado et al. [129] for an U.S. FDA and EMA approved drug product.

Within the last decade, efforts have been made to integrate and fully use the benefits of NIR spectroscopy in the emerging field of continuous production processes. Since continuous pharmaceutical manufacturing settings aim for real-time release, the CQAs of intermediates and final drug product need to be constantly monitored, preferably by level-1 control, which directly adapts process parameters according to real-time measurement [130].

Several examples of NIR probes within continuous manufacturing in academic research as well as in industrial settings have been reported. Chablani et al. inserted an NIR probe in the vacuum transfer line from the six-segmented fluid-bed incorporated in GEA Pharma

Systems' ConsiGma™ unit on a production scale (cf. section 1.1.4) to measure the moisture content of the dried granules (up to 1.06 %) after discharge [104]. Fonteyne et al. recorded at-line data on granules produced by the same continuous production line and correlated them to moisture contents of 3.9–6.76 % determined by Karl Fischer titrations [131], and finally applied a PLS model based on the last NIR spectra collected in-line in one of the cells [132]. Despite good accuracy in the range of approx. 3.5–7.8 % residual moisture, the monitoring of granule drying in real-time was impeded by fouling of the sensor surface, and predictions were limited to the drying end point instead of the entire process [133].

Nevertheless, the company Vertex has demonstrated the feasibility of replacing conventional moisture determination of samples with real-time moisture testing of dried granules within the transfer module after fluid-bed granulation in a continuous manufacturing line [134] using a set-up similar to the one described by Chablani et al. [104].

Despite being supported by the authorities, some disadvantages of NIR spectroscopy cannot be denied. The most obvious are the limited penetration depth, which was found to be lower than 0.75 mm above 1600 nm wavelength in the diffuse reflectance mode [135], and the necessity for chemometric data evaluation, making the method a “black box” without proper staff training. Current software facilitates the selection of spectral pre-treatments with minimal understanding but thereby also poses the risk of invalid results due to unknown variables [136]. The dual dependence on chemical and physical properties can be perceived as a mixed blessing. On the one hand, it even allows to different states of water molecules within a solid material to be distinguished [137] or water content and particle size to be determined simultaneously. On the other hand, properties such as particle size interfere when they are not the property of interest and need to be additionally evaluated or compensated. Fouling is also a disadvantage that needs provisions when applying NIR spectroscopy for in-line determination [14, 138, 139]. The latitude of countermeasures presented during recent years illustrates the extent of the problem. Physical countermeasures such as probe air purging systems [140], complex probe-immersion and retracting mechanisms, including the possibility of cleaning the probe with detergents or solvents (e.g. GEA Pharma Systems' Lighthouse Probe™) [141], as well as mathematical correction of affected spectra [142] have been proposed. All in all, the advantages of fast, reliable and non-destructive sample analysis

combined with regulatory acceptance surely outweigh the method's disadvantages, since provisions to minimize disturbing effects are available.

1.2.3.4.2. Other methods

Within the regulated pharmaceutical industry, decisions concerning employed analytical tools are typically made based on available guidelines, compendial monographs and the regulatory advice. The aim is to provide maximum security of method acceptance. Taking into consideration the upfront investments in analyzers, data processing and necessary staff training/ hiring, this risk-averse mindset is quite understandable. Consequently, NIR spectroscopy is more than one step ahead of competing technologies for moisture content determination of pharmaceutical bulk solids. Nevertheless, other methods have been employed and reported for real-time moisture monitoring in academic research.

An example of an alternative technique is NMR spectrometry, which has a strong analytical potential, since it is a non-contact and non-destructive method, and has already been proven to be suited for on-line moisture measurements from 0–14% on moving coal in the early 1960s [143]. Reports of successful moisture measurement can be found in the field of food technology [144, 145], and static measurements on hard capsules have allowed to distinguish subtypes of adsorbed water. Despite being a powerful tool and the availability of cryogenic free sample-treatment techniques, NMR spectrometry must step back with regards to cost and the requirement for an external magnetic field, both of which limit applicability, especially for on-line or in-line applications [146].

A different approach to moisture measurement in fluid-bed processes is the utilization of acoustic emission (AE). Probes situated within the product bowl capture acoustic emissions originating from the particle movement and related collision and friction either with other particles or with the product bowl [147]. Audible sounds are detected by a microphone and high-frequency sounds over 100 kHz are monitored by acoustic emission sensors that incorporate piezoelectric transducers. A portion of these high-frequency sounds, called elastic waves, propagates differently through solid matter and air, in which they are attenuated. Since these waves are not disturbed by background noise, their measurement by accelerometers forms the underlying principle of acoustic emission measurements [148].

While some scientific papers correlating acoustic emissions to the moisture content are available, most reports establish a closer correlation with the particle size in the fluidized bed than with the moisture content [149]. Halstensen et al. [150] could, for example, only predict general production trends by using the method combined with a calibration comprising 900 urea granulation trials instead of a precise moisture content. The

relatively poor correlations are suggested to be the reason for limited acceptance and industrial preference for other methods, particularly NIR spectroscopy.

Triboelectric probes have been suggested for on-line or in-line moisture monitoring measuring the current intensity and fluctuations generated by the impact of fluidized particles on a metal probe inserted in the process stream [151], and electrical capacitance tomography (ECT), which measures the difference in permittivity of the processed material by two electrodes and subsequently correlates it to the moisture content [152], has also been suggested as an alternative method in literature. However, future work would be necessary for the industrial application of either of the presented systems, since reports do not extend beyond the proof-of-concept stage.

1.3. Microwave technology

1.3.1. Basic principle

Measurements by microwave sensors are based on the interaction between microwaves and the material under test which forms the medium of propagation of the electromagnetic waves. The interaction in the form of reflection, refraction, scattering, absorption or change of phase and speed is utilized to determine physical properties of the tested material [153]. One of these properties is the moisture content.

1.3.2. Physical background

Water molecules of adsorbed or added water are randomly oriented within solid particles. As dipolar molecules, they attempt to align with its orientation, if an external, oscillating electromagnetic field is applied. Dependent on the frequency of the applied field, their motions are either too slow to follow the change in orientation, they move at the required rate or they remain apparently unaffected. In dielectric analysis, which is the principle behind MRT sensor systems, the response of a material under the influence of the alternating electric field is measured. It is described by the complex relative permittivity:

$$\epsilon_r = \epsilon' - j \epsilon''.$$

In this equation, ϵ' is the real and ϵ'' the imaginary part (j is the imaginary unit). The real part ϵ' is also called dielectric constant and is a measure of the extent of polarization, which the material undergoes once an electromagnetic field is applied. The imaginary part ϵ'' , or dielectric loss-factor, is a measure of the ability of the material to dissipate electrical energy in form of heat [89]. In addition, materials are often characterized by a dissipation factor or loss tangent, $\tan \delta$, which is defined as

$$\tan \delta = \epsilon'' / \epsilon',$$

and represents the fraction of incoming energy that is dissipated as heat [154]. The frequency-dependency of the complex relative permittivity of a pure polar substance such as water is exemplarily depicted in Figure 5.

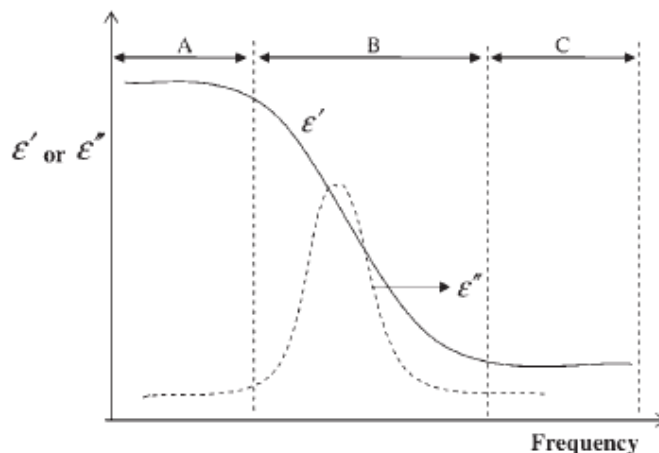


Figure 5: Dielectric dispersion of a pure polar substance (from [155]).

If the applied electric field is of low frequency (region A), the polar molecules have sufficient time to orientate in accordance to the direction of field changes as their relaxation time is shorter than the interval of field reverse. They can partially neutralize the electrical charges induced by the electric field. This leads to a charge storage by the polar molecules demonstrated by a high dielectric constant [155]. With increasing frequency, the time interval of the field reverse starts to accelerate and equalize with the relaxation time. Upon further acceleration, dipoles start to lag behind the alternating field in their movement, which causes the dielectric constant to decline. At the same time, dielectric loss exhibits a peak as energy is absorbed and dissipated (region B). At even higher frequencies, the interval for change of field direction is even shorter than the relaxation time of the molecules. Hence, they cease to adapt and remain unchanged resulting in a low extent of polarization and a low energy dissipation (region C) [155].

Since the dielectric constant of water at ambient conditions is remarkably higher ($\epsilon' \sim 80$ at 2 GHz [154]) compared to the dielectric constants of dry, organic materials such as typical pharmaceutical excipients (e.g. $\epsilon' < 3$ at 2 GHz for MCC and maize starch [156, 157]), the material's dielectric properties heavily rely on the moisture content. This relationship can be exploited to determine the moisture of a material non-destructively and in real-time.

As the influence of a dielectric material on the applied electromagnetic field depends on the mass of the measured material and hence the total number of interacting water molecules, the density of the material being tested also plays an important role. Therefore,

density has to be kept constant or density influence has to be removed mathematically. Either sample preparation may be required to obtain similar density [158], they can also be circumvented by a two parameter measurement:

In the case of MRT sensor systems, a resonator is loaded with the material under test and the increase of stored energy decreases the frequency of the associated resonance mode compared to the resonance frequency in air ($\Delta f = f_0 - f_1$), whereas the dissipation of electrical energy as heat leads to an attenuation of the resonance curve which is associated to a relative widening of the curve compared to the curve in air ($\Delta B = B_1 - B_0$). The described effects are depicted in Figure 6.

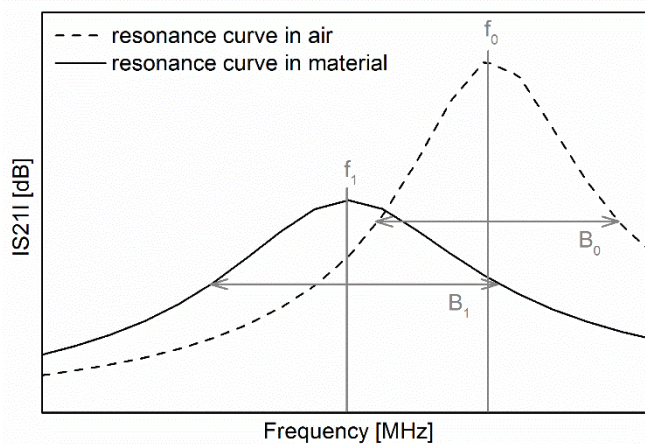


Figure 6: Measurement factors. $|S21|$ = scalar voltage gain, f_0 = resonance frequency in air, f_1 = resonance frequency in material, B_0 = bandwidth in air, B_1 = bandwidth in material (from [159]).

Bandwidths and frequencies of the material under test as well as those of an unloaded sensor system are recorded. Since both parameters, the lowering of the resonance frequency as well as the bandwidth broadening depend in an equal manner on density changes but to a different extent on the moisture content, the density's influence can be eliminated by building the ratio of both [160, 161]:

$$M(\Psi) = (B_1 - B_0) / (f_0 - f_1) = \Delta B / \Delta f.$$

The values of the resulting moisture function $M(\Psi)$ can then be correlated to the reference moisture of a material determined by direct methods to establish a model for moisture prediction. Hence, microwave resonance sensors can determine the moisture content of moving samples in flowing material streams of varying density after correlation with reference moistures. This qualifies them as a PAT tool for real-time in-line moisture monitoring in production processes.

Compared to previously described systems such as NIR spectroscopy, the penetration depth is expanded to the lower centimeter range as the frequency range utilized in MRT measurements is sufficiently high in order to exclude ionic influences below 1 GHz but

also lower than the molecular relaxation frequency of water at approx. 20 GHz at ambient conditions [154]. The resulting wavelengths are relatively long and thereby allow complete moisture content determination of physically bound water not only on the surface, but also in the core. Crystal water, in contrast, is not detected as the frequency and energy of the applied microwaves are not able to translate or rotate water molecules in crystals [81].

1.3.3. Applications of microwave sensors

1.3.3.1. Applications in other industries

Microwave sensor systems have been used for decades for quality control within several industrial branches. Independent of their arrangement, the sensitivity towards water molecules makes the measurement of moisture content one of the most important applications of microwave sensing. The scientific discipline to investigate solids and liquids containing water by identifying their properties in microwave fields is also referred to as “microwave aquametry” [89]. In practice, most applications aim to quantitatively determine the water content in these solids and liquids.

As in other branches of science and industry, the interest in microwave aquametry increased with the availability of microwave moisture meters at reasonable cost which was linked to the inexpensive availability of solid state components in the late 1970s [89] and the introduction of microprocessors into measuring devices in the 1980s [153].

An important industry that looked into electrical properties for fast and non-destructive moisture measurement already in the early 20th century is the agricultural industry. While early techniques such as the measurement of the resistance between two electrodes in a sample [162] required at least insertion of electrodes, later studies placed samples of wet materials in the path of an electromagnetic wave between horn antennas and could easily determine the moisture by establishing a simple relationship between propagation constant and water content. Advantages such as the larger penetration depth that enables sampling of more representative volumes, the non-necessity of physical contact to the sample, the relative insensitivity towards environmental conditions such as dust and the nondestructive nature of the method and hence its great potential for agricultural applications became obvious [90]. Extensive reviews on dielectric measurements starting from first quantitative measurements in the 1950s up to current trends have been published. Among these, especially the historical review by Okamura [163] as well as the reviews by Nelson [164, 165] and Kraszewski [89, 90, 166], which were both heavily involved in microwave research at the U.S. Department of Agriculture spanning from

quality control applications up to research on plant structures, have to be mentioned. In a more recent review, also the feasibility and advantages of density independent moisture measurements were discussed for agricultural applications [167]. In general, agricultural microwave sensing nowadays spans from free-space moisture and density determination of grain and oilseed [168] over the determination of the same properties of peanuts before shelling [169] up to the recently demonstrated density-independent moisture measurement on free-flowing samples of oat [170], corn, wheat and soybeans [171].

A closely-related industrial branch is food industry. Here, reports on microwave moisture sensing include the measurement of dielectric properties as a quality attribute of treated fish [172] or the judgement on the maturity of fruits and vegetables [165] but the full potential is again deployed in the case of moisture measurements. If a food product has to be dried in order to increase the shelf life, moisture determination by microwave sensors should confirm a sufficiently low moisture content. Typical examples include, the drying of green tea leaves [173], or, as mentioned above, the drying of peanut [169] and hazelnut [174] kernels under a certain moisture limit prior to storage in order to minimize the aflatoxin risk. Other important tasks are the quality control during the processing of tobacco [175, 176] and coffee. In coffee industry, the beans exhibit extremely low moistures after roasting and are cooled down by water. Hence, appropriate setting of moisture content as near as possible to the specified limits is required to maximize profitability but excessive humidification has to be excluded to prevent the product from becoming moldy [177]. Here, optimized measurement systems that eliminate the density-dependence of results by a two-parameter measurement [178] are available, for example, for measurements on conveyer belts. The tobacco industry utilizes the sensitivity towards moisture and density. Besides moisture measurement, which can be conducted by passing the product through a resonator hollow space [179], microwave sensors are able to measure the density and control the cutting of the rods at appropriate positions in cigarette production [177].

Since the last decades, microwave moisture meters also made their entrance into wood processing industry. In addition to moisture measurements of veneer sheets [180] or sawdust [181], sensor systems were employed to grade the strength of structural timber based on the local moisture distribution and number of knots [182]. Tailor-made measurements solutions suited for the measurements of veneer sheets or particle board provide information on moisture content, density and presence of air inclusions [183].

Special industrial sensors which operate based on a combination of transmission and resonance method consist of two probes and products are guided through the gap between them and measured contactless. The system can easily be installed in production line, and the material under test is scanned for moisture content in real-time at up to 1000 measurements per second [184]. This setup can be transferred to various processes which continuously produce band- or plate-shaped materials that should be controlled for moisture or density like polymer foils, veneer or paper.

The actual applicability of microwave sensors for moisture monitoring is even broader. Possible fields of application that were reported recently include the measurement of moisture content of milk powder in the dairy processing industry [185], moisture measurement of flowing biomass pellets [186], or even the moisture content investigation of ancient stone materials in cultural heritage objects such as buildings [187], but microwave sensors are not as prevalent in these sectors as in the previously discussed ones.

1.3.3.2. Pharmaceutical applications

While microwave sensors were already accepted for moisture content determination in various industries, reports from the heavily regulated pharmaceutical industry did not arise until 2006. In this year, one of the earliest applications of microwave techniques in the pharmaceutical sector was reported by Gradinarsky et al. [156]. His group, originating from AstraZeneca's center of excellence for PAT, employed an open-ended coaxial probe to measure the moisture content during high-shear granulation. One year later, Melichar described approaches to employ MRT as an off-line tool for laboratory measurements on pharmaceutical raw materials focusing his work on the characterization of measurement parameters and accuracy of the method [158]. Another year later, the in-line application of MRT in fluidized-bed processes has been introduced by Buschmüller et al., who claimed time-savings of up to 75 % during final drying phase using the sensor system [188]. However, limitations in moisture determination accuracy above approx. 8 % moisture content of the material under test were found in subsequent studies [81, 189, 190]. Comparable limitations were already observed by Gradinarsky et al. using the open-ended coaxial probe at levels above 14 % moisture content but were attributed to temperature and granule size increases with granulation time.

Nevertheless, the MRT sensor introduced by Buschmüller et al., meanwhile commercially available, has been employed for in-line granule moisture assessment over a limited range in several fluid-bed granulation studies [191–193]. A similar MRT sensor has also been

compared to a NIR sensor system during at-line use on powders and tablets at up to 5 % moisture and convinced with accurate determinations upon a simultaneous reduction of calibration efforts [194]. This investigation was confirmed when comparing MRT and NIR sensors for in-line moisture (up to 5.5 %) and density determination on ribbons in a roller compaction process [195].

After the benefits of multiple resonance sensors were reported in 2010 [160], a new generation of MRT sensor systems for pharmaceutical applications emerged over the last few years. At first, a planar MRT sensor, which was operating at six resonances in the range of 2–8 GHz, was reported by a group from Purdue University [196]. It proved able to measure the chemical composition of MCC, water and acetaminophen blends but the tested moisture range did not go beyond 6.5 %. In a second report by the same group, a microwave resonant cavity was designed and employed to determine the density, acetaminophen content and moisture content (up to 5 %) of ribbons within a continuous dry granulation line [197]. Hence, by focusing on other properties than moisture and by measuring the moisture content of rather dry granules or inherently dry ribbons generated by roller compaction, first multiple resonance sensor systems for pharmaceutical use did not fully exploit the benefits of the multiple resonances in this regard.

After considerations on the extension of measurement ranges and the provision of a dual-frequency MRT sensor system, first steps to unambiguously determine moisture contents above 8 % were published in 2014 by Kollar et. al. [198]. The tested system operated at resonances of 2.5 and 8.5 GHz and the authors proposed sectional data interpretation exhibiting a threshold at 15 % moisture content, which resulted in scattering values around this threshold.

1.4. Aims of the thesis

MRT sensor systems for in-line moisture measurements in pharmaceutical fluid-bed granulation processes are rather new as compared with NIR sensor systems employed for this purpose. The limited number of reports on this technology have provided a proof-of-concept but have also listed the limitations of available systems: the increasing deviation between moisture contents measured by MRT and reference values at higher moisture contents has been described, and the threshold between precise and imprecise measurements has been found to depend on granule composition. Generally speaking, the cause has not been fully investigated and no measures have been taken to circumvent this limitation. Furthermore, a comparison with NIR spectroscopy, which is the main competing PAT tool for moisture monitoring and the internationally accepted “gold standard”, has not yet been provided.

Primary aim of this thesis was therefore to explore and understand the root cause of these limitations in order to overcome them for broad range moisture determination. Based on different sets of studies, an improved sensor system should be qualified for at-line use, carefully investigated and adapted for in-line application in different equipment types and compared with NIR spectroscopy as the most prominent PAT tool for moisture monitoring.

Subdivided according to the following chapters, the particular aims were:

- To explore and understand material and resonance mode related restrictions of first-generation sensor systems by investigating of raw resonance curves, and to prove the validity of at-line measurements conducted using a newly developed multi-resonance system within the former measurement range and beyond based on specifications stated in ICH Q2(R1).
- To optimize the acquisition rate and treatment of data collected by the previously qualified multi-resonance sensor systems to allow in-line application during lab-scale granulations of drug-free formulations.
- To test the performance of the sensor system during in-line moisture measurement of granulations comprising a crystal water containing excipient and an API under conditions faced during process development.
- To demonstrate the applicability of novel multi-resonance MRT sensors in pilot-scale equipment and to compare different statistical approaches to calibrate the system.
- To compare multi-resonance MRT sensors with NIR spectroscopy focusing on performance, ease of application and potential synergies in a semi-continuous granulation process.

1.5. Outline of the thesis

In this thesis, different aspects of the application of microwave resonance technology sensor systems for moisture measurements in fluid-bed equipment are investigated.

The first chapter provides a background of the current state of research in the fields of fluid-bed granulation, such as the investigated unit operation, moisture content analysis as the task to be performed and microwave resonance technology as the method of choice to perform this task and to be optimized within this work. In the context of moisture content analysis, NIR spectroscopy is introduced and discussed in order to understand its application.

The second chapter reveals a deeper insight into the inherent limitations of resonance frequencies employed by commercially available sensor systems. For the first time, raw resonance curves measured on pharmaceutical excipients are provided and studied to investigate the root cause of ambiguous microwave moisture values recorded by first-generation sensor systems. These curves are complemented by measurements at higher resonances which are enabled by a newly developed multi-resonance MRT sensor system. The design of the introduced multi-resonance sensor is described and an MLR model based on microwave moisture values is established for moisture quantitation. The system is validated according to ICH guideline Q2(R1) for off-line or at-line moisture quantitation of a granule formulation in the range of up to 20 % moisture, providing a major prerequisite for routine application in the pharmaceutical industry.

Following method validation for at-line application, the fitness for purpose of the previously introduced multi-resonance MRT sensor system to measure granule moisture in-line during laboratory scale fluid-bed granulation of a drug-free formulation is evaluated in the third chapter. To meet the requirements of measuring chaotically moving solid particles under highly variable temperature conditions in real-time, certain amendments of the data acquisition rate and temperature compensation are introduced. A 40-second averaging window is identified as the best compromise between smooth data and the possibility of rapid intervention, if required. MLR models based on density-independent microwave moisture values and reference values obtained by loss on drying and Karl Fischer titration are elaborated, applied and compared. It is found that reliable processes monitoring up to at least 14 % granule moisture are feasible and that deviating process trajectories can easily be detected in real-time.

The fourth chapter is designed to ascertain the suitability of the multi-resonance MRT sensor to determine water content in more realistic drug formulations comprising crystal-water containing material and an active pharmaceutical ingredient. Initially, examinations of raw resonance curves measured off-line on lactose monohydrate samples are conducted in a similar manner to those previously described for starch and microcrystalline cellulose. Interferences between the additional higher resonance frequencies and crystal water are thereby excluded. In the second part of this chapter, in-line measurements on a donepezil hydrochloride formulation being qualitatively similar to a marketed drug product against dementia are performed during granulations featuring process parameters set according to a 2^3 full factorial experimental design. Successful calibration and validation of an MLR predictive model for moisture content are hence conducted simultaneously to process development without additional material or time consumption, highlighting the ease of application of MRT sensor systems. The resulting model comprises the entire moisture range (up to 10 %) faced during granulations containing the employed excipients and API.

A crucial requirement for PAT tools, such as the described multi-resonance MRT sensor, is universal applicability in different types of devices of an equipment family. In addition, such tools should facilitate upscaling and thus be mountable from developmental to production scale equipment. Therefore, the last two chapters comprise further application-oriented research based on the fundamentals established in the previous chapters.

Within the fifth chapter, the multi-resonance MRT sensor is employed for in-line moisture monitoring in a pilot-scale bottom-tangential-spray fluidized bed granulator. This fluid-bed apparatus is designed to process a 10- to 15-times larger product volume than the previously employed granulator and differs in terms of more directed rotational product movement and location of the spraying nozzle. A smaller inlet in the product bowl demands a reconstructed version of the MRT sensor featuring a smaller sensor head and additional inlets are incorporated in the product bowl and screened to optimize data acquisition. The optimized mounting position results in halving the averaging window to 20 seconds, which leads to even tighter process control. Moisture prediction models covering the full range up to 16 % product moisture, based on more sophisticated chemometric methods such as PCR and PLS, are developed and compared with MLR regarding predictive abilities and applicability.

Finally, the implementation into a continuous manufacturing set-up, which is a main field of the application of PAT tools, is investigated in chapter six. The reconstructed MRT sensor is mounted in a semi-continuous fluid-bed dryer equipped with NIR probes. This setting allows the first reported direct comparison of in-line moisture measurement by both methods. The suitability of multi-resonance MRT sensor systems and NIR probes to serve as redundant sensor systems with different operating principles measuring the same CQA is elucidated. Interferences are excluded and both PAT tools reliably measure the entire drying process from 12 % down to 5 % granule moisture in this setting. Comparisons in the range up to 20 % granule moisture enable judgement of the advantages and disadvantages of both systems and verify that moisture monitoring by MRT sensor systems is a valuable alternative to NIR spectroscopy, providing great ease of application.

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

This chapter introduces a novel multi-resonance microwave sensor system using additional resonances over a wider frequency band compared to established systems. The sensor was employed to investigate inherent limitations of commercially available first-generation sensor systems operating at a single resonance, in addition to material-related limitations. Therefore, raw resonance curves obtained by measuring two commonly employed pharmaceutical excipients (MCC and maize starch) and their behavior at various moisture levels were studied before the system was used for moisture measurement of granule samples containing both excipients. A multiple linear regression (MLR) prediction model built by correlating microwave moisture values to the moisture determined by Karl Fischer titration could be established and employed. Since the validation of an analytical method is a major prerequisite for its application in the pharmaceutical industry, a systematic method validation approach examining all relevant characteristics specified in ICH guideline Q2(R1) was, for the first time, conducted for water content quantitation by microwave resonance technology sensor systems.

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Evaluation of authorship:

Co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Johanna Peters	0	60	66	66	75
Wolfgang Taute	0	20	34	20	0
Claas Döscher	20	10	0	0	0
Kathrin Bartscher	20	0	0	0	0
Michael Höft	20	0	0	14	0
Reinhard Knöchel	20	0	0	0	15
Jörg Breitzkreutz	20	10	0	0	10

The project idea was generated by C. Döscher, K. Bartscher, M. Höft, R. Knöchel and J. Breitzkreutz. The study design was mainly developed by J. Peters. W. Taute and C. Döscher contributed by design of the novel microwave resonance sensor system which is one of four parts of the results section and essential prerequisite for the remaining parts, J. Breitzkreutz contributed to the design of the systematic method validation. The experimental part of the sensor design was conducted by W. Taute, experimental work for all parts focusing on sensor application was conducted by J. Peters. Evaluation of results was conducted by J. Peters using computational algorithms for signal collection and processing written by W. Taute based on his discussions with M. Höft. The draft of the manuscript was written by J. Peters and proof-read by all co-authors. R. Knöchel substantially contributed to the content of the sections dealing with the sensor design and the physical principles behind it, J. Breitzkreutz substantially contributed to the complete manuscript.

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

Johanna Peters^{a,b}, Wolfgang Taute^c, Kathrin Bartscher^b, Claas Döscher^d, Michael Höft^c, Reinhard Knöchel^c, Jörg Breitzkreutz^a

^a Heinrich–Heine–University Düsseldorf, Institute of Pharmaceutics and Biopharmaceutics, Düsseldorf, Germany

^b NextPharma Waltrop, Pharbil Waltrop GmbH, Waltrop, Germany

^c Christian–Albrechts–University Kiel, Institute of Electrical Engineering and Information Technology, Kiel, Germany

^d Döscher Microwave Systems GmbH, Hamburg, Germany

Analytica Chimica Acta, Volume 961, Pages 119–127 (doi: [10.1016/j.aca.2017.01.021](https://doi.org/10.1016/j.aca.2017.01.021))

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.

3. In-line moisture monitoring in fluidized bed granulation using a novel multi-resonance microwave sensor

This chapter describes the first in-line application of the novel multi-resonance microwave sensor system that was introduced and qualified for off-line or at-line purposes in the previous chapter. The sensor system was mounted in a laboratory scale fluid-bed granulator and data on all four available resonances were collected during exemplary placebo granulations. Different options to realize an accelerated data acquisition rate and the suitability of the arithmetically implemented temperature compensation were investigated and adapted to achieve rapid and reliable in-line moisture determination in wet granulation processes. Based on the calculation of density-independent microwave moisture values and reference moistures obtained by Karl Fischer titration as well as loss on drying, MLR models were constructed and applied. Proof-of-concept for the detection of deviating process trajectories could be provided during an independent test set.

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Evaluation of authorship:

Co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Johanna Peters	0	40	80	60	70
Kathrin Bartscher	20	10	0	5	0
Claas Döscher	20	10	0	5	5
Wolfgang Taute	0	10	20	20	5
Michael Höft	20	10	0	5	5
Reinhard Knöchel	20	10	0	5	5
Jörg Breitzkreutz	20	10	0	0	10

The project idea was generated by K. Bartscher, C. Döscher, M. Höft, R. Knöchel and J. Breitzkreutz. The study design was mainly developed by J. Peters based on detailed discussions among all authors. The experimental part was conducted by J. Peters after in-depth discussions with W. Taute who performed numerous preliminary experiments at the Institute of Electrical Engineering and Information Technology in Kiel. Evaluation of results was conducted by J. Peters using computational algorithms for signal collection and processing written by W. Taute. Results of initial evaluations were optimized based on their discussions with K. Bartscher, C. Döscher, M. Höft and R. Knöchel. The draft of the manuscript was written by J. Peters and proof-read by all co-authors. C. Döscher, W. Taute, M. Höft and R. Knöchel substantially contributed to the content within the sections measurement principle, sensor design and by provision of the simulation of electric field strength distribution shown as Figure 1. J. Breitzkreutz substantially contributed to the complete manuscript.

In-line moisture monitoring in fluidized bed granulation using a novel multi-resonance microwave sensor

Johanna Peters^{a,b}, Kathrin Bartscher^b, Claas Döscher^c, Wolfgang Tauted^d, Michael Höft^d, Reinhard Knöchel^d, Jörg Breitzkreutz^a

^a Heinrich–Heine–University Düsseldorf, Institute of Pharmaceutics and Biopharmaceutics, Düsseldorf, Germany

^b NextPharma Waltrop, Pharbil Waltrop GmbH, Waltrop, Germany

^c Döscher Microwave Systems GmbH, Hamburg, Germany

^d Christian–Albrechts–University Kiel, Institute of Electrical Engineering and Information Technology, Kiel, Germany

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Abstract: Microwave resonance technology (MRT) is known as a process analytical technology (PAT) tool for moisture measurements in fluid-bed granulation. It offers a great potential for wet granulation processes even where the suitability of near-infrared (NIR) spectroscopy is limited, e.g. colored granules, large variations in bulk density. However, previous sensor systems operating around a single resonance frequency showed limitations above approx. 7.5 % granule moisture. This paper describes the application of a novel sensor working with four resonance frequencies. In-line data of all four resonance frequencies were collected and further processed. Based on calculation of density-independent microwave moisture values multiple linear regression (MLR) models using Karl–Fischer titration (KF) as well as loss on drying (LOD) as reference methods were build. Rapid, reliable in-process moisture control (RMSEP \leq 0.5 %) even at higher moisture contents was achieved.

4. Moisture monitoring in fluid-bed granulation by multi-resonance microwave sensor: applicability on crystal-water containing Donepezil granules

Up to now, all experiments presented within this thesis have been based on moisture measurements on excipients or combinations thereof. Additionally, employed excipients did not contain crystal water. Therefore, the main purpose of the following chapter was to provide evidence that multi-resonance microwave sensors are suited to the determination of water content in formulations with crystal-water containing material and an active ingredient.

Possible influences of crystal water were evaluated by investigation of raw resonance curves of all four resonances obtained by off-line measurements of lactose monohydrate. Measurements were conducted using the multi-resonance microwave sensor described in previous chapters.

In the second part of this chapter, the same sensor system was employed for in-line determination of moisture content in laboratory-scale fluid-bed granulations of formulations containing lactose monohydrate and donepezil hydrochloride, which were qualitatively similar to a marketed drug product against dementia. Development and validation of a predictive model were conducted during a 2^3 full factorial design process DoE, which served to study the influence of process parameters on selected quality attributes of resulting granules. Thus, sensor performance on real-life formulations and under conditions faced during process development, a key requirement for sensor application in pharmaceutical drug product development, could be thoroughly assessed.

The following research paper has been published by AAPS PharmSciTech (Impact Factor 2017: 2.666) in 2019. The research presented in this article has partially been conducted in the context of the project “Prozessanalytische Technologie für die Hormon-Granulierung” that was funded by the German Federal Environmental Foundation (Deutsche Bundesstiftung Umwelt, DBU, Project No. 30816). J. Peters, W. Taute, C. Döscher, M. Höft, R. Knöchel and J. Breitreutz were fully involved in the project and are therefore listed as authors on all papers based on research conducted in terms of this project.

Evaluation of authorship:

Co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Johanna Peters	25	50	100	60	70
Wolfgang Taute	0	10	0	20	5
Claas Döscher	12.5	10	0	5	5
Michael Höft	12.5	10	0	5	5
Reinhard Knöchel	12.5	10	0	5	5
Jörg Breitreutz	37.5	10	0	5	10

The work described in the manuscript can be divided in off-line measurements on lactose monohydrate as a crystal-water containing filler which were performed within the framework of the aforementioned project and in in-line measurements during granulations of donepezil hydrochloride which were conducted after the end of the project. The overall project idea was generated by C. Döscher, M. Höft, R. Knöchel and J. Breitreutz and already included the intention to perform measurements on crystal-water containing material. The idea of in-line measurements during an experimental design on granulations of donepezil hydrochloride originated from discussions between J. Breitreutz and J. Peters. The study design was mainly developed by J. Peters based on detailed discussions among all authors. The experimental part was conducted by J. Peters. Evaluation of results was conducted by J. Peters using computational algorithms for signal collection and processing written by W. Taute. Results of initial evaluations were optimized based on discussions with all project partners. The draft of the manuscript was written by J. Peters and proof-read by J. Breitreutz who substantially contributed to the complete manuscript. All co-authors proof-read the second draft of the manuscript and contributed to the content by their remarks and suggestions.

Moisture monitoring in fluid-bed granulation by multi-resonance microwave sensor: applicability on crystal-water containing Donepezil granules

Johanna Peters^a, Wolfgang Taute^b, Claas Döscher^c, Michael Höft^b, Reinhard Knöchel^b, Jörg Breitzkreutz^a

^a Heinrich-Heine-University Düsseldorf, Institute of Pharmaceutics and Biopharmaceutics, Düsseldorf, Germany

^b Christian-Albrechts-University Kiel, Institute of Electrical Engineering and Information Technology, Kiel, Germany

^c Döscher Microwave Systems GmbH, Hamburg, Germany

AAPS PharmSciTech (2019) 20: 6 (doi: [10.1208/s12249-018-1209-7](https://doi.org/10.1208/s12249-018-1209-7))

Abstract: Multi-resonance microwave sensors have recently been introduced for moisture monitoring of pharmaceutical particulates up to > 20 % residual moisture. The extended measuring range compared to previous systems as well as the microwave moisture values' independence of other physical attributes make them promising PAT tools for various pharmaceutical production processes. However, so far research focused on measurements on raw materials or drug-free model granulates and has neither evaluated the applicability for materials with crystal water containing excipients nor for active ingredients. In this study, possible influence of crystal water was evaluated using lactose monohydrate and donepezil hydrochloride, an active pharmaceutical ingredient (API) against dementia. The study clearly showed that the contained hydrate does not cause interferences and is not monitored by the applied frequencies. Material-related limits measuring lactose monohydrate were only observed above typical granulation moistures and could be explained using raw resonance curves. Furthermore, the inclusion of donepezil hydrochloride into the monitored formulations and varied process parameters demonstrated the versatility of the microwave resonance sensor system. Inlet air temperature, spraying rate and air flow were varied according to a 2³ full factorial experimental design. A predictive model (R² 0.9699, RMSEC: 0.33 %) could be established using samples produced with different process parameter settings adjusted according to the corner points of the full factorial design and validated on the center point granulation processes (RMSEV: 0.38 %). Thereby performance on actual formulations and conditions faced during process development could be thoroughly assessed and hence, another key requirement for applicability in formulation development could be met.

5. From laboratory- to pilot-scale: moisture monitoring in fluidized bed granulation by a novel microwave sensor using multivariate calibration approaches

As a next step toward the demonstration of universal applicability, a multi-resonance microwave sensor system was employed for in-line moisture monitoring in a pilot-scale bottom-tangential-spray fluidized bed granulator. In comparison with the almost identical fluid-bed devices employed in the two preceding chapters, the processable product volume of this fluid-bed device was enlarged by a factor of approx. 10–15, and the setup differed by the employment of a special bottom-spray technique combined with a guided airflow, resulting in rotational particle movement (cf. section 1.1.3). Thus, typical industrial challenges that occur upon installation of a PAT probe in pilot- or commercial scale-equipment were faced. The equipment changes demanded sensor head reconstruction, resulting in a reduced diameter of < 5 cm and reevaluation of the sensor's mounting position.

Finally, the optimized mounting position permitted acceleration of the measurements, and models for moisture prediction based on multiple linear regression, as well as more sophisticated principal component regression (PCR) and partial least squares regression (PLS), were built and investigated with respect to their predictive abilities and their applicability in routine moisture monitoring.

The following research paper has been published by Drug Development and Industrial Pharmacy (Impact Factor 2017: 1.883) in 2018. The research presented in this article has been conducted in the context of the project “Prozessanalytische Technologie für die Hormon–Granulierung” that was funded by the German Federal Environmental Foundation (Deutsche Bundesstiftung Umwelt, DBU, Project No. 30816). J. Peters, W. Taute, C. Döscher, M. Höft, R. Knöchel and J. Breitzkreutz were fully involved in the project and are therefore listed as authors on all papers based on research conducted in terms of this project.

Evaluation of authorship:

Co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Johanna Peters	0	50	66	50	70
Wolfgang Taute	0	10	34	20	0
Claas Döscher	25	10	0	10	0
Robin Meier	0	0	0	0	5
Michael Höft	25	10	0	10	5
Reinhard Knöchel	25	10	0	10	10
Jörg Breitzkreutz	25	10	0	0	10

The overall project idea was generated by C. Döscher, M. Höft, R. Knöchel and J. Breitzkreutz and already included the intention to perform measurements in a pilot-scale bottom-tangential spray fluid-bed granulator. The study design was mainly developed by J. Peters based on detailed discussions with W. Taute, C. Döscher, M. Höft, R. Knöchel and J. Breitzkreutz during project meetings and calls. The experimental part was conducted by J. Peters who received comprehensive support during granulation trials from engineers of L. B. Bohle’s service center. W. Taute performed numerous preliminary experiments at the Institute of Electrical Engineering and Information Technology in Kiel and accompanied parts of the granulation trials conducted at L. B. Bohle’s service center for troubleshooting and adjustment of the sensor setup. Evaluation of results was conducted by J. Peters using computational algorithms for signal collection and processing written by W. Taute. Results of initial evaluations were optimized based on discussions with C. Döscher, M. Höft and R. Knöchel. The draft of the manuscript was written by J. Peters. J. Breitzkreutz and R. Knöchel substantially improved individual manuscript sections during their revision. All co-authors proof-read the second draft of the manuscript and R. Meier and M. Höft contributed by their approval and remarks.

From laboratory- to pilot-scale: moisture monitoring in fluidized bed granulation by a novel microwave sensor using multivariate calibration approaches

Johanna Peters^a, Wolfgang Taute^b, Claas Döscher^c, Robin Meier^d, Michael Höft^b, Reinhard Knöchel^b, Jörg Breitzkreutz^a

^a Heinrich-Heine-University Düsseldorf, Institute of Pharmaceutics and Biopharmaceutics, Düsseldorf, Germany

^b Christian-Albrechts-University Kiel, Institute of Electrical Engineering and Information Technology, Kiel, Germany

^c Döscher Microwave Systems GmbH, Hamburg, Germany

^d L.B. Bohle Maschinen + Verfahren GmbH, Ennigerloh, Germany

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Abstract: Recently, microwave resonance technology (MRT) sensor systems operating at four resonances instead of a single resonance frequency were established as a process analytical technology (PAT) tool for moisture monitoring. The additional resonance frequencies extend the technologies' possible application range in pharmaceutical production processes remarkably towards higher moisture contents. In the present study, a novel multi-resonance MRT sensor was installed in a bottom-tangential-spray fluidized bed granulator in order to provide a proof-of-concept of the recently introduced technology in industrial pilot-scale equipment. The mounting position within the granulator was optimized to allow faster measurements and thereby even tighter process control. As the amount of data provided by using novel MRT sensor systems has increased manifold by the additional resonance frequencies and the accelerated measurement rate, it permitted to investigate the benefit of more sophisticated evaluation methods instead of the simple linear regression which is used in established single-resonance systems. Therefore, models for moisture prediction based on multiple linear regression (MLR), principal component regression (PCR) and partial least squares regression (PLS) were built and assessed. Correlation was strong (all $R^2 > 0.988$) and predictive abilities were rather acceptable (all RMSE ≤ 0.5 %) for all models over the whole granulation process up to 16 % residual moisture. While principal component regression provided best predictive abilities, multiple linear regression proofed as a simple and valuable alternative without the need of chemometric data evaluation.

6. Real-time process monitoring in a semi-continuous fluid-bed dryer – microwave resonance technology versus near-infrared spectroscopy

The trend toward continuous manufacturing in the pharmaceutical industry has spurred the implementation of PAT tools. While drug products produced in traditional batch processes are released based on analytical end-product testing, the goal of continuous processing is real-time product release. Conformity of intermediate and end-product properties to the quality target product profile (QTPP) needs to be monitored closely along the manufacturing route. To minimize the risk of deviations and guarantee early identification and diversion of out-of-specification material, even in the case of sensor malfunctions or maintenance, redundant measurements by different PAT tools are required.

Within this chapter, the suitability of multi-resonance MRT sensor systems and NIR probes to serve as redundant sensors with different operating principles measuring the same CQA was tested. The prototype MRT sensor introduced in the previous chapter was mounted in a semi-continuous fluid-bed dryer, which was part of L. B. Bohle's continuous manufacturing line (c.f. section 1.1.4) and equipped with NIR probes in each of its four drying cells. Granule moisture was monitored using both methods, and the results were examined with respect to possible interferences. Successful in-line moisture monitoring throughout an entire process within a (semi-)continuous drying unit has not yet been published for either NIR sensors or for microwave resonance systems. Moreover, the setup allowed the first direct comparison of both sensor systems in a fluid-bed process.

The following research paper has been published by the International Journal of Pharmaceutics (Impact Factor 2017: 3.862) in 2018. The research presented in this article has been conducted as a continuation study in the context of the project “Prozessanalytische Technologie für die Hormon-Granulierung” which was funded by the German Federal Environmental Foundation (Deutsche Bundesstiftung Umwelt, DBU, Project No. 30816). J. Peters, W. Taute, C. Döscher, M. Höft, R. Knöchel and J. Breitkreutz were fully involved in the project and are therefore listed as authors on all papers based on research conducted in terms of this project.

Evaluation of authorship:

Co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Johanna Peters	14	60	66	60	70
Andreas Teske	14	15	34	5	5
Wolfgang Taute	14	5	0	15	0
Claas Döscher	14	5	0	5	0
Michael Höft	14	5	0	5	5
Reinhard Knöchel	15	5	0	5	10
Jörg Breitkreutz	15	5	0	5	10

The idea behind this manuscript originated during project meetings and discussions by all authors. The study design was mainly developed by J. Peters based on detailed discussions with A. Teske and optimized based on suggestions of all authors. The experimental part was conducted by J. Peters who received comprehensive support of A. Teske during the trials which were all performed at L. B. Bohle’s technology center. Evaluation of results including resonance curves obtained by the microwave sensor and NIR signals was conducted by J. Peters. For interpretation of the resonance curves, computational algorithms for signal collection and processing written by W. Taute were employed. Results of initial evaluations were optimized based on discussions with all authors. The draft of the manuscript was written by J. Peters. J. Breitkreutz and R. Knöchel substantially improved individual manuscript sections during their revision. All co-authors proof-read the second draft of the manuscript and A. Teske and M. Höft contributed by their remarks and suggestions.

Real-time process monitoring in a semi-continuous fluid-bed dryer – microwave resonance technology versus near-infrared spectroscopy

Johanna Peters^a, Andreas Teske^b, Wolfgang Tautec, Claas Döscher^d, Michael Höft^c, Reinhard Knöchel^c, Jörg Breitzkreutz^a

^a Heinrich–Heine–University Düsseldorf, Institute of Pharmaceutics and Biopharmaceutics, Düsseldorf, Germany

^b L.B. Bohle Maschinen + Verfahren GmbH, Ennigerloh, Germany

^c Christian–Albrechts–University Kiel, Institute of Electrical Engineering and Information Technology, Kiel, Germany

^d Döscher Microwave Systems GmbH, Hamburg, Germany

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Abstract: The trend towards continuous manufacturing in the pharmaceutical industry is associated with an increasing demand for advanced control strategies. It is a mandatory requirement to obtain reliable real-time information on critical quality attributes (CQA) during every process step as the decision on diversion of material needs to be performed fast and automatically. Where possible, production equipment should provide redundant systems for in-process control (IPC) measurements to ensure continuous process monitoring even if one of the systems is not available. In this paper, two methods for real-time monitoring of granule moisture in a semi-continuous fluid-bed drying unit are compared. While near-infrared (NIR) spectroscopy has already proven to be a suitable process analytical technology (PAT) tool for moisture measurements in fluid-bed applications, microwave resonance technology (MRT) showed difficulties to monitor moistures above 8 % until recently. The results indicate, that the newly developed MRT sensor operating at four resonances is capable to compete with NIR spectroscopy. While NIR spectra were preprocessed by mean centering and first derivative before application of partial least squares (PLS) regression to build predictive models (RMSEP = 0.20 %), microwave moisture values of two resonances sufficed to build a statistically close multiple linear regression (MLR) model (RMSEP = 0.07 %) for moisture prediction. Thereby, it could be verified that moisture monitoring by MRT sensor systems could be a valuable alternative to NIR spectroscopy or could be used as a redundant system providing great ease of application.

7. Conclusion and future perspectives

7.1. Benefits of the new-generation microwave sensor systems

The limited measurement range of first-generation microwave sensor systems for moisture monitoring operating at a single resonance frequency of 2–3 GHz has been an obstacle for in-line application in pharmaceutical granulation processes. The unambiguously determinable moisture range enabled detection of drying end-points or tracking relatively dry processes, but sensor systems failed to precisely deliver relevant information. They provided microwave moisture values as output signals but no explanation of deviations between them and the reference values at higher moisture contents was available. The underlying measurement principle was known but detailed investigations could not be realized. Therefore, systems could be regarded as “black boxes”.

Since signal recognition and evaluation were performed using different algorithms, the newly introduced MRT sensor system, operating at four resonance frequencies, could be employed to investigate and understand material and resonance frequency-related limitations by evaluation of raw resonance curves. The non-linear increase in microwave moisture values $M(\Psi)$ and the later absence of a further increase with increasing material moisture could be attributed to minimum decreases and no visible damping observed on raw resonance curves. The investigation of resonance curves also confirmed that this effect is material-dependent and occurs at higher moisture contents with increasing frequencies. Thus, the design of the novel sensor using additional resonances over a wide frequency band turned out to be a useful adaptation to extend the range of measurable moisture. Hence, it could be successfully applied to the measurement of higher moisture levels (e.g. up to 30 % in the case of maize starch and up to 20 % in granule formulations) at-line or in-line and thereby covers all levels usually present in pharmaceutical fluid-bed processes.

Despite of the more sophisticated sensor design, adaptations to the system could be made with manageable effort, so that similar sensors were employed in lab-scale, pilot-scale and continuously operating manufacturing equipment. In all applications, it was confirmed that multi-resonance sensor systems reliably measure process moisture in real-time over the entire range.

7.2. Method validation according to ICH guideline Q2(R1)

The method validation of a sensor system according to internationally adopted guidelines, such as the ICH guideline Q2(R1), is crucially important to gain broader acceptance of a new PAT tool in the pharmaceutical industry. The multi-resonance MRT sensor was validated for off-line or at-line moisture quantitation of granules samples. In the context of the above-mentioned guideline, quantitation of water in the sample corresponds to the assay of a selected component of a medicinal product. Following implementation of an MLR model, a systematic validation approach comprising measurements by different operators, different analysis dates and different ambient conditions was carried out according to the protocol outlined in the guideline. Despite the parameter reproducibility, which was inapplicable due to the unique nature of the novel sensor prototype and issues with moisture stability of samples during robustness measurements, all data were fully consistent with the formal requirements.

Compliance with the requirements demonstrates the ability of the system to produce reliable data and thereby paves the way for routine use. In addition, it is a major prerequisite for achieving regulatory approval to replace laboratory analytics with the PAT tool.

7.3. Applicability in pharmaceutical development and routine manufacturing

The capability of multi-resonance MRT moisture sensors to correctly and precisely determine the moisture content during fluid-bed processes has been proven off-line and in three different measurement settings within this thesis. All moisture values that arose in the different processes could be adequately linked to residual moisture contents of the material under test. Hence, the range of interest could be fully monitored employing this technology. Solely in the case of drying processes within the semi-continuous fluid-bed dryer starting with relatively wet material (20 % moisture content), limitations were faced that could be attributed to fouling. The deposit automatically detached once the expected moisture from twin-screw granulations was reached.

In all cases of in-line application, a temperature compensation was established and complemented by an appropriate averaging window, which was selected to obtain smooth curves but still ensure rapid intervention if aberrating process trajectories were recorded. Depending on the equipment scale, measurement position and resulting material coverage of the sensor head, averaging periods of 20–70 seconds were found to ensure

high-quality predictions exhibiting root mean square errors of less than 0.5 %. In general, the efforts required to implement multi-resonance microwave sensors in a production setting were found to be manageable. Although modifications of the sensor head were necessary to fit in measurement ports of smaller size, the resulting quality of predictions in larger scale equipment appeared to be even better, which could be attributed to the excellent material coverage.

Calibrations of the sensor system were easily constructed based on MLR of microwave moisture values to readings of reference measurements. These could be recorded during a single granulation or drying process conducted for calibration purposes resp. measured on samples taken during this process. The use of loss on drying as a reference method instead of the more time-consuming and expensive Karl Fischer titration was not found to be detrimental to the prediction quality. Despite uncomplicated calibration, models resulted that were able to compete or outperform more sophisticated chemometric approaches such as PLS and PCR. In particular, it should be noted that a combination of two resonance frequencies, namely the lowest and a higher one, often seemed to be a sweet spot between measurability of high moistures and large penetration depth, resulting in the most suited models. This constitutes a good approach for further simplification.

Comparison with NIR spectroscopy finally highlighted the relevance of the system. The MRT sensor system delivered precise predictions and at least equal results for all model performance indicators. This paves the way for acceptance as a genuine alternative to NIR sensors, which are the most prominent example of PAT tools, but still have critical weaknesses that cannot easily be eliminated, such as the dual dependence of spectra on physical and chemical properties and the limited penetration depth. The urgent need for additional and simpler systems triggered by the trend towards continuous manufacturing strengthens these aspects.

Summarizing the observations made during the various application studies, multi-resonance microwave sensors were assessed to generally satisfy the demands placed on in-line moisture measurement in current pharmaceutical development and manufacturing processes. They ensure continuous process verification and tracking of a highly critical quality attribute in wet granulation independent of its equipment or scale.

7.4. Critical considerations and open questions

Besides all the advantages of multi-resonance microwave sensor systems highlighted within this thesis, there remain several critical issues that need to be addressed in order to provide a complete overall picture.

Although the majority of the discussed applications describes in-line applications, the method validation of the newly developed MRT sensor was conducted during at-line use. This does not indicate inappropriateness for the production of reliable moisture predictions during in-line application, but can rather be attributed to the lack of specific regulatory advice on the validation of in-line PAT methods. The ICH guideline Q2(R1) appears to have been designed for conventional methods, such as liquid chromatography, and the extent of parameters that should be tested can only be realized on stationary samples. However, it was demonstrated that moisture measurement by multi-resonance microwave sensors is robust and fit for its intended purpose by comparison with conventional LOD determination and Karl Fischer titration. The relative performance of the method was evaluated over a broad range of moistures and temperatures, indicative of linearity and range resp. robustness of the method.

Another point for discussion and optimization in the case of future sensor developments is the size relationship between the ring-shaped metallic strip forming the resonator and the entire sensor head. Upon reconstruction of the sensor head for application in smaller ports, the diameter of the metallic ring strip embedded in the sensor head was only marginally reduced, while the total diameter of the sensor head was reduced by a greater extent, resulting in a smaller distance between the ring strip and the edge of the sensor head. Thus, the electromagnetic stray field corresponding to the sensing zone not only projected directly out of the sensor head towards the material under test but also laterally to the sensor. As a result, measurements were not fully independent of their surroundings and a new temperature compensation needed to be established for each equipment. However, the first sensor prototype employed in chapters 2–4 demonstrated that a single temperature compensation is universally applicable in the case of adequate sensor head design. Frequencies and bandwidths recorded in air were the same whether they were recorded within a granulator or not.

Regarding the evaluation method, it would be interesting to further investigate the best option for the utilization of the high precision of the lowest resonance frequency in the lower moisture range. Current studies solely focus on a universally applicable evaluation

method, providing acceptable, small deviations over the entire range. Up to the point where microwave moisture values did not further increase linearly with moisture content, it was noted that employing the lowest resonance frequency produced the most accurate results. It is assumed that this is associated with its deeper penetration depth as compared with higher resonances. While segmental analysis was tested in preliminary investigations, setting the right threshold to change between different analytical models proved difficult, since fluctuating values resulted around it. All in all, this should be regarded as a point for additional optimization rather than as an uncontrolled factor, since the deviations between predicted and reference values were rather small in the lower moisture range, even though a combination of several resonance frequencies was employed.

Considerably more work will be needed in case the MRT sensor system should be employed in routine analysis. Up to now, analytical data have been captured and processed into frequencies and bandwidths using custom-written MATLAB® algorithms, microwave moisture values have been calculated in Microsoft® Excel using VBA scripts and model development, calibration and prediction of measured data have been conducted using either Microsoft® Excel or chemometric software packages. Online prediction and analysis were not realized with respect to which feedback control and real time product release were also out of reach. All in all, the multidimensional data would need to be collected and stored appropriately by 21 CFR Part 11-compliant software, their retention would need to be GMP-compliant and the whole system would need to be qualified for in-line use.

It must be noted that execution of these tasks would require a cross-functional team and is only a prerequisite in the case of sensor application for continuous process verification or even for quality control targeting parametric release of GMP-batches. Since the extent of method validation of PAT tools should be commensurate with the intended use, these expenses can be reduced to a minimum in the case of application to developmental batches. In this case, the current sensor setup can already substantially increase the process understanding substantially.

7.5. Future perspectives

Microwave resonance technology sensor systems are an emerging tool within the present PAT establishment in the pharmaceutical industry. Within this thesis, the advantages of multi-resonance microwave sensors for moisture monitoring in fluid-bed processes have been systematically demonstrated. Benefits as well as limitations have been identified and

the in-depth understanding and extension of the measurable moisture range should decrease the regulatory burden for acceptance as a PAT tool.

Triggered by the trend toward continuous manufacturing, the implementation of PAT tools within pharmaceutical manufacturing has made huge progress within recent years. Regulatory authorities nowadays not only endorse the implementation of systems to ensure that processes constantly deliver product of acceptable quality, but also provide additional guidance by new or adapted monographs and guidelines. The goal of parametric release creates an incentive to implement PAT tools and MRT sensor systems could be a valuable alternative, providing great ease of application as compared with NIR spectroscopy. In particular, the announced ICH guideline Q13 on continuous manufacturing could provide a clearer implementation landscape and eventually further accelerate implementation of control strategies relying on redundant systems measuring the same CQA by different analytical in-line methods based on different physical principles, as currently discussed by the AAPS' PAT focus group.

It is expected that future work using the resonance system described within this thesis may take one step back from using all four resonances in the case that further studies confirm that models based on microwave moisture values from two resonance frequencies provide the same accuracy and further simplify data interpretation. Additionally, it is not mandatory that data interpretation at the level of raw resonance curves can be accessed by operators. In future, there may be different operator levels that provide access to these data upon model development and method validation but do not make them available during routine use, where the microwave moisture values and resulting calculated moisture contents suffice. In addition, these measures could also limit the size of data, which would be necessary for transmittance into the process control system.

With regard to other areas of application, it may be worth to investigating the MRT sensor's fit for purpose to monitor organic granulations and organic fluid-bed coatings. In particular titanium dioxide in rutile form, which is commonly used in coating processes, exhibits an even higher permittivity than water. Therefore, an evaluation of process monitoring in (organic) coatings containing this excipient could be promising to identify MRT sensor systems as an alternative to Raman spectroscopy. This would allow method circumvention in case discussions on possible energy input by intensive laser radiation that could induce degradation of single components arise.

Another possible area of application could be the moisture measurement within the production of orodispersible films. In this case, modified sensor heads, which are already employed in the veneer and foil industry, would be recommended. In a production line, a gap sensor, which guides the measuring field through the film-formed sample, could be installed following casting of the wet film in a webbed form and conveying through an oven for drying and prior to being rolled to form the jumbo roll for intermediate storage.

In addition, the microwave resonance sensor system may be suited to non-destructive measurement of the porosity of tablets in the case that a moisture-independent calibration can be elaborated, since porosity measurements on non-pharmaceutical samples have already been reported. Depending on the volume of tablets to be measured, a reconstruction of the measurement setup and sensor head would also be necessary in this case. Furthermore, various applications in processes that identify moisture content as a critical quality attribute of the processed material could be interesting tasks.

8. Summary

The application of novel microwave resonance technology sensor systems as a PAT tool for moisture measurement within pharmaceutical fluid-bed granulation and drying processes was studied within this thesis. While commonly employed in the food and wood processing industries, the technology is still emerging within the pharmaceutical sector and its use has stagnated in recent years.

One of the most relevant limitations of first-generation sensor systems operating at a single resonance frequency, namely deficient performance at moisture ranges higher than 8 %, was examined, and a novel multi-resonance microwave sensor aiming to overcome these issues was investigated. For the first time within the pharmaceutical sector, raw resonance curves were recorded and evaluated at various moisture levels. A link between the absence of further attenuation resp. relative widening of the resonance curve and a non-linear increase in microwave moisture values at higher moistures could be established. This off-line characterization revealed that measurable ranges depend on the employed resonance frequency and the material under test, exemplary shown for MCC and maize starch. Since moisture levels expected to result from wet granulations were fully covered, it provided a sound basis for later sensor application to process monitoring. The characterization was complemented by off-line measurements on granule samples of up to approx. 20 % residual moisture content conducted during a successful method validation according to ICH guideline Q2(R1).

In a following step, necessary adaptations were made to employ the sensor system for in-line measurements. The temperature compensation could be verified within the employed small-scale granulator, the measurement rate was accelerated, and a sliding average window was applied to measured frequencies and bandwidths in order to compensate for random fluctuations caused by varying material coverage. Similar to off-line measurements, an MLR model covering all moisture contents occurring during the process (up to 14 %) could be successfully developed and validated, and even its value in the detection of aberrating granule moistures was proven in an independent test set.

To confirm the promising results also on crystal-water containing formulations, measurements on raw resonance curves were extended to lactose monohydrate. While concerns regarding interactions between crystal-water and higher resonance frequencies

could be remedied, it was found that optimum results can only be ensured up to approx. 12.5 % residual moisture. Since granule formulations containing lactose monohydrate are usually processed at relatively low moistures to avoid dissolving of larger portions, this range was considered fully adequate. During in-line measurements, which were part of an experimental design, donepezil hydrochloride was additionally employed to provide experimental evidence on real-life formulations and to prove robustness independent of the conditions faced during process development on a laboratory scale.

Since experiments have focused on relatively similar small-scale equipment so far, and the demonstration of universal applicability has been rated as crucial, the sensor system was also mounted on a fluid-bed granulator of pilot-scale size featuring a bottom-tangential-spray setup. Typical industrial challenges that occur upon installation of novel PAT tools, such as a necessary reconstruction of the sensor head to fit in a smaller opening of the product container and a tricky selection of the measurement position, have effectively been overcome. Further optimization of the mounting position resulted in increased material coverage of the sensor head, which allowed the averaging window to be halved, thereby tightening process control. In this context, different chemometric methods to build moisture prediction models up to the highest process moistures of approximately 16 % were investigated with respect to predictive abilities and user-friendliness. While PCR models exhibited the best overall performance, the simplicity and comparable quality of prediction encouraged consideration of simple linear combinations of microwave moisture values of two resonances for future use.

Since PAT tools provide the cornerstone for movement toward real-time release in continuous pharmaceutical manufacturing, and respective equipment will become a main area of application, one of the novel sensor prototypes was tested in a semi-continuous fluid-bed dryer, which was integrated as part of a full-scale continuous manufacturing line. Proof-of-concept could be provided without further adaptations of the sensor head or position. Additionally, the availability of NIR sensors within the drying unit enabled the first in-line comparison of MRT and NIR spectroscopy. The comparative study revealed that, in particular, the simple calibration by a linear combination of the microwave moisture values of two resonances makes multi-resonance MRT sensor systems a valuable alternative to NIR spectroscopy. The applicability of both sensors within a single process chamber highlighted their combination as an example of non-interfering redundant

sensors which could ensure early detection in the case of drifts or malfunction and a high level of independency, since both operate based on different physical principles.

The results of the present thesis confirm that multi-resonance MRT sensor systems reliably measure the moisture content of bulk solids during off-line, at-line and in-line applications. In-depth investigations regarding deficiencies of previous systems were possible based on raw resonance curves and allowed the reliable identification of the measurable range, which was significantly extended as compared with previous systems. During application studies in three different equipment types, the value of the novel MRT sensors as a PAT tool was confirmed. Simple and reliable data evaluation methods were identified.

9. Zusammenfassung

Im Rahmen der vorliegenden Arbeit wurden neuartige Mikrowellenresonanzsensoren als PAT-Werkzeug für die Feuchtemessung in pharmazeutischen Wirbelschichtprozessen untersucht. Während das Verfahren bereits häufig z.B. in der Nahrungsmittel- und in der Holzverarbeitenden Industrie eingesetzt wird, ist es im pharmazeutischen Bereich noch eine in der Entwicklung befindliche Technologie, deren Anwendung in den letzten Jahren stagnierte.

Eine der wesentlichen Einschränkungen der mit einer Resonanzfrequenz arbeitenden Mikrowellensensoren der ersten Generation war die unzureichende Vorhersageleistung in Feuchtebereichen oberhalb von 8 %. Ein Mehrfrequenzsensor, der auf einem grundsätzlich neuen Aufbauprinzip beruht, wurde präsentiert, um diese Einschränkungen zu untersuchen und zu überwinden. Der verwendete Sensor-Prototyp wurde mit Software bedient, die – zum ersten Mal im pharmazeutischen Umfeld – die Aufnahme und Auswertung der Rohdaten (Resonanzkurven) auf verschiedenen Feuchteniveaus ermöglichten. Dadurch konnte ein Zusammenhang zwischen dem Ausbleiben weiterer Dämpfung bzw. weiterer Verbreiterung der Resonanzkurven und somit der nicht-linearen Zunahme von Mikrowellenfeuchtwerten bei höheren Feuchten etabliert werden. Die off-line Charakterisierung führte zu der Annahme, dass der messbare Feuchtebereich sowohl von der eingesetzten Resonanzfrequenz als auch von dem eingesetzten Material, in diesem Fall mikrokristalline Cellulose oder Maisstärke, abhängig ist. Da die in einer Feuchtgranulation erwarteten Restfeuchten vollständig durch ein off-line etabliertes Vorhersagemodell abgedeckt wurden, bildete dieses eine gute Grundlage, um den Sensor zu einem späteren Zeitpunkt für die Prozesskontrolle einzusetzen. Die Charakterisierung des Systems wurde mit einer Methodvalidierung entsprechend der ICH-Guideline Q2(R1) vervollständigt, die erfolgreich off-line an Granulatmustern mit bis zu 20 % Restfeuchtegehalt durchgeführt wurde.

In einem weiteren Schritt wurden Anpassungen vorgenommen, die es ermöglichen, das Sensorsystem für in-line Messungen einzusetzen. Hierzu wurde einerseits die Güte der Temperaturkompensation innerhalb des verwendeten Granulators im Labormaßstab verifiziert, andererseits die Aufnahmezeit beschleunigt. Da trotz beschleunigter Aufnahmen durch die stark schwankende Materialbeladung auch schwankende Messwerte auftraten, wurde eine Mittelung der gemessenen Frequenzen und Bandbreiten nötig.

Genau wie im Fall der off-line Messungen, konnte mittels multipler linearer Regression ein den kompletten auftretenden Feuchtebereich abdeckendes Prognosemodell entwickelt und validiert werden. Im Gegensatz zu vorherigen Sensorsystemen konnten Produktfeuchten bis zu 14 % zuverlässig bestimmt werden. Weiterhin ermöglichte das erstellte Modell eine frühe Detektion von Abweichungen. Während des Einsatzes in einer Granulation im Labormaßstab konnte so bereits eine abweichende Granulatfeuchte und damit ein zugrundeliegender Sprühfehler gegen Ende der Sprühphase entdeckt werden.

Um die vielversprechenden Resultate auch an kristallwasserhaltigen Formulierungen zu testen, wurden zusätzlich Messungen an Lactose-Monohydrat durchgeführt. Hierbei konnten Bedenken hinsichtlich Interaktionen zwischen Kristallwasser und hohen Resonanzfrequenzen ausgeräumt werden, die Übereinstimmung zwischen gemessenen und Referenzfeuchten war jedoch maximal bis zu 12.5 % optimal. Da Formulierungen mit Lactose-Monohydrat üblicherweise bei moderaten Feuchten granuliert werden, um das Lösen von zu großen Anteilen zu vermeiden, reicht dieser Bereich aus, um Prozesse vollständig zu überwachen. Während in-line Messungen, die im Rahmen einer statistischen Versuchsplanung durchgeführt wurden, wurde zusätzlich der Wirkstoff Donepezil-Hydrochlorid eingesetzt. Dadurch sollte einerseits die Eignung des Sensors an einer praxisnahen Formulierung und andererseits die Robustheit der Messungen bei verschiedenen vorgegebenen Prozessbedingungen, die während der Formulierungsentwicklung im Labormaßstab auftreten können bzw. bewusst getestet werden, überprüft werden.

Um nach den bisherigen Untersuchungen in ähnlichen Geräten im Labormaßstab die universelle Einsatzmöglichkeit des Sensorsystems zu überprüfen, wurde dieses in einer weiteren Studie in einem Wirbelschichtgranulator im Pilotmaßstab, der nach dem Bottom-Tangential-Spray-Verfahren arbeitet, eingebaut. Typische Herausforderungen, die im Rahmen der industriellen Implementierung eines neuen PAT-Werkzeugs auftreten wie z.B. die Anpassung des Sensorkopfes an einen kleineren Messstutzen oder die Auswahl der Messposition, konnten erfolgreich gemeistert werden. Durch die Optimierung der Messposition konnte die Materialbeladung während der Messung erhöht werden. Hierdurch wurde eine Halbierung des Mittelungsintervalls möglich, was wiederum eine noch engmaschigere Prozesskontrolle erlaubt. Zusätzlich wurden verschiedene chemometrische Methoden zur Feuchtevorhersage im Bereich bis zur höchsten Prozessfeuchte von 16 % hinsichtlich der Güte der Vorhersage und des Bedienkomforts

verglichen. Während PCR Modelle die beste Gesamtleistung erbrachten, ermutigten die Einfachheit und vergleichbare Vorhersagegüte einer Linearkombination aus Mikrowellenwerten lediglich zweier Resonanzfrequenzen, diese als Alternative für zukünftige Auswertung in Betracht zu ziehen.

Da PAT-Werkzeuge ein Schlüssel zu der in der kontinuierlichen Fertigung angestrebten Echtzeitfreigabe darstellen und entsprechendes Produktionsequipment ein Haupteinsatzgebiet aktueller Sensorsysteme werden wird, wurde der Einsatz des Sensor-Prototyps in einem semikontinuierlichen Wirbelschichttrockner, der Teil einer kontinuierlichen Produktionslinie im Produktionsmaßstab war, untersucht. Die Anwendbarkeit des Systems konnte ohne weitere Anpassungen des Messkopfes oder der Messposition demonstriert werden. Zusätzlich ermöglichten die in der Wirbelschicht-Trocknungseinheit verbauten NIR-Sensoren den ersten in-line Vergleich von Mikrowellenresonanztechnologie und NIR-Spektroskopie. Die vergleichende Studie zeigte, dass mehrfrequente Mikrowellenresonanzsensoren insbesondere durch die einfache Kalibrierung anhand einer Linearkombination der Mikrowellenwerte zweier Resonanzfrequenzen eine wertvolle Alternative zu zur NIR-Spektroskopie darstellen. Die gleichzeitige Anwendung beider Messsysteme in einem Produktbehälter machte deutlich, dass keine Interferenzen auftreten und die Kombination beider Technologien eine Möglichkeit bietet, Fehlfunktionen oder Drifts früh und aufgrund verschiedener zugrundeliegender physikalischer Prinzipien auch sicher und unabhängig voneinander zu erkennen.

Zusammenfassend bestätigen die Resultate dieser Dissertation, dass mit Hilfe mehrfrequenter Mikrowellenresonanzsensoren sowohl off-line und at-line als auch in-line zuverlässig die Restfeuchte von Schüttgütern bestimmt werden kann. Darüber hinaus erlaubten Untersuchungen an Rohdaten, die Schwächen vorheriger Systeme zu erkennen und den im Vergleich zu vorherigen Sensoren deutlich ausgeweiteten Messbereich eindeutig einzugrenzen. Durch die Verwendung gleichartiger Sensoren in verschiedenen Gerätetypen konnte der Nutzen des neuartigen Messsystems als PAT-Werkzeug bestätigt werden. Zuverlässige Auswertemethoden konnten etabliert werden.

10. List of original publications

J. Peters, W. Taute, K. Bartscher, C. Döscher, M. Höft, R. Knöchel, J. Breitzkreutz
Design, development and method validation of a novel multi-resonance microwave sensor for moisture measurement

Analytica Chimica Acta, 961 (2017) 119–127

J. Peters, K. Bartscher, C. Döscher, W. Taute, M. Höft, R. Knöchel, J. Breitzkreutz
In-line moisture monitoring in fluidized bed granulation using a novel multi-resonance microwave sensor

Talanta, 170 (2017) 369–376

J. Peters, W. Taute, C. Döscher, R. Meier, M. Höft, R. Knöchel, J. Breitzkreutz
From laboratory-to pilot-scale: moisture monitoring in fluidized bed granulation by a novel microwave sensor using multivariate calibration approaches

Drug Development and Industrial Pharmacy, 44 (2018) 961.

J. Peters, A. Teske, W. Taute, C. Döscher, M. Höft, R. Knöchel, J. Breitzkreutz
Real-time process monitoring in a semi-continuous fluid-bed dryer-microwave resonance technology versus near-infrared spectroscopy

International Journal of Pharmaceutics, 537 (2018) 193–201.

J. Peters, W. Taute, C. Döscher, M. Höft, R. Knöchel, J. Breitzkreutz
Moisture monitoring in fluid-bed granulation by multi-resonance microwave sensor: applicability on crystal-water containing donepezil granules

AAPS PharmSciTech, (2019) 20: 6

11. Contributions to meetings

11.1 Oral presentations

J. Peters, K. Bartscher, J. Breitzkreutz

Investigation on energy consumption and potential savings during bulk production of an oral contraceptive

8th Annual PSSRC Symposium, Ljubljana, Slovenia, 16.–18.09.2014

J. Peters, K. Bartscher, J. Breitzkreutz

Inline moisture monitoring in fluid-bed granulation using a novel multi-frequency microwave sensor

9th Annual PSSRC Symposium, Ghent, Belgium, 16.–18.09.2015

J. Peters, K. Bartscher, C. Döscher, W. Taute, P. Harbaum, H. Rehbaum, R. Knöchel, J. Breitzkreutz

From laboratory to pilot scale: Inline moisture monitoring in fluid bed granulation using microwave resonance technology

10th Annual PSSRC Symposium, Copenhagen, Denmark, 06.–08.07.2016

J. Peters, K. Bartscher, C. Döscher, W. Taute, P. Harbaum, H. Rehbaum, R. Knöchel, J. Breitzkreutz

From laboratory to pilot scale: Use of microwave resonance technology for inline moisture monitoring in fluid bed granulation

EuPAT, 8th pan-European QbD and PAT Science Conference, Cork, Ireland, 03.–04.10.2016

11.2 Poster presentations

J. Peters, B. Kollar, C. Kindermann, K. Bartscher, C. Döscher, J. Breitzkreutz

Novel inline moisture measurement in fluid-bed granulation for energy, material and time savings

9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lisbon, Portugal, 31.03.–03.04.2014

J. Peters, K. Bartscher, C. Döscher, W. Taute, M. Höft, R. Knöchel, J. Breitzkreutz

Use of a novel multi-frequency microwave sensor for inline moisture monitoring in fluid-bed granulation

AAPS Annual Meeting and Exposition, Orlando, USA, 25.–29.10.2015

J. Peters, K. Bartscher, W. Taute, C. Döscher, M. Höft, R. Knöchel, J. Breitzkreutz

A novel PAT-tool in fluid bed granulation: moisture monitoring by a multi-frequency microwave sensor

10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Glasgow, UK, 04.–07.04.2016

J. Peters, K. Bartscher, C. Döscher, W. Taute, P. Harbaum, H. Rehbaum, R. Knöchel, J. Breitzkreutz

From laboratory to pilot scale: Use of microwave resonance technology for inline moisture monitoring in fluid bed granulation

EuPAT, 8th pan-European QbD and PAT Science Conference, Cork, Ireland, 03.–04.10.2016

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