In-line monitoring of granule moisture in fluidized bed granulators using microwave resonance technology as novel PAT tool

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Abbreviations

API	Active pharmaceutical ingredient
B_E	Frequency bandwidth
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CL PVP	Crospovidone
CPP	Critical process parameter
DoE	Design of Experiments
e.g.	For example
EMEA	European Medicines Agency
EP	European Patent
Eq	Equation
EU	European Union
FDA	Food and Drug Administration
f_E	Resonance frequency
ff_c	Flowability function
Fig	Figure
FMEA	Failure Mode Effect Analysis
GHz	Gigahertz
GMP	Good manufacturing practice
hrs	Hours
ICH	International Conference on Harmonization
ISM band	Industrial, Scientific, Medical band
JP	Japanese Pharmacopoeia
KF	Karl Fischer titration
KF w/o cw	Karl Fischer without crystal water
LOD	Loss on drying
LOD/IR	Loss on drying caused by infrared light exposure

max	Maximum
MCC	Microcrystalline cellulose
m_d	Mass of the dry substance
MHz	Megahertz
min	Minutes
m/m	Mass/mass
MRT	Microwave Resonance Technology
mW	Milliwatt
m_w	Mass of water
MW	Microwave value
MVA	Multivariate Data Analysis
m^3/h	Cubic meter/hour
n	Number of measurements
NIR	Near-infrared spectroscopy
NMR	Nuclear Magnetic Resonance Spectroscopy
PAT	Process analytical technology
PCA	Principal Component Analysis
Ph. Eur.	European Pharmacopoeia
PLS1	Projection of Latent Structures
PPMS	Partially pregelatinized maize starch
SD	Standard deviation
sec	Seconds
SEM	Scanning electron microscopy
w/o	Without

A Introduction

The American Food and Drug Administration (FDA) published in 2004 a regulatory framework to encourage pharmaceutical companies to implement process analytical technologies (PAT) in production processes [FDA 2004]. The desired aims of the PAT approach are to design, analyze and control manufacturing processes by measuring critical process parameters (CPP) which affect critical quality and performance attributes. By identifying the CPPs of a process and by monitoring them, preferably in-line or on-line, product quality is ensured.

On long-term considerations, the implementation of PAT shall merely enable real-time release, to enhance process understanding and to increase automation.

The implementation of the PAT approach in pharmaceutical fluidized bed granulation processes was tracked within the present study.

The residual water content of a granule is an eminently critical process parameter during wet granulation processes. It significantly affects critical quality attributes, e.g. the stability of the active pharmaceutical ingredient (API), granule hardness, particle size distribution and dissolution behaviour. Furthermore, subsequent manufacturing steps like compression to tablets are influenced by granule moisture. Granules with high residual water content may lead to poor flow properties.

To ensure product quality, and to meet the FDA's PAT approach, the real-time measurement of granule moisture throughout fluidized bed processes is required. Up until now, the moisture content of wet granules has been monitored by either indirect parameters, e.g. exhaust air temperature, or by discontinuous water determination. The water determination by measuring the loss on drying, preferably by infrared light exposure (LOD/IR), or Karl Fischer titration (KF) are well established off-line measuring tools. Due to sample withdrawal and process interruptions for external analysis, these methods are associated with a loss of time and hence, an uncertainty of the results. It is impossible to obtain real-time control using these off-line techniques.

For the in-line determination of granule moisture, only a few analytical technologies are available which meet the FDA's PAT approach. Several attempts to make use of infrared (IR) and near-infrared (NIR) spectroscopy have been reported [Methfessel 2006, Mattes 2005, Rantanen 2001, Wildfong 2002, Watano 1991, 1994, 1996]. The short wavelength and the associated high reflections of radiation and low penetration depth are disadvantageous for reliable moisture determination. Granule particles adhering to the measuring window due to fouling may interfere with water determination as the radiation is reflected. The company Glatt reported in 1997 about first approaches to use the one parameter microwave resonance technique for the determination of granule moisture during fluidized bed processes.

The methods used as in-line tools so far have significant limitations. All methods depend strongly on the total amount of measured particle layers and the product density. Consequently, a direct correlation with the water content of the tested material is not possible yet.

In order to obtain reliable real-time moisture monitoring a density independent measuring technique is a mandatory precondition.

Beyond the pharmaceutical industry, the two parameter microwave resonance technique is a well established method for moisture determination in various industrial areas (e.g. timber and tobacco industry). Due to the simultaneous determination of frequency shift and damping of the microwaves, it enables the continuous, density independent, moisture monitoring of moving bulk solids in real-time.

The aim of this study was to develop a microwave resonance sensor system that is in accordance with the current guidelines of Good Manufacturing Practice (cGMP). Subsequently, the sensor system should be implemented in a fluidized bed apparatus. The practical application of the MRT sensor for in-line moisture determination and control of fluidized bed processes should be investigated.

In particular it should be investigated, whether the type of the water contained in a product, crystal-water or weakly bound water, has an impact on moisture measurement by MRT, particularly with regard to requirements on calibration.

The main focus should be on the endpoint determination of the drying process and the real-time control of entire fluidized bed granulation processes using MRT as in-line measuring tool.

Subsequently, it should be tested, if substances with swelling and water absorbing characteristics, such as crospovidone, affect the MRT water determination.

Furthermore, it is of great interest, to what extend additional data such as product temperature and density signals, delivered by the MRT sensor system, are helpful to improve process understanding and to ensure product quality.

B General issues

1 Process Analytical Technology

Process analytical technology (PAT) is one main issue of the "Pharmaceutical cGMPs for the 21st Century" published by the American Food and Drug Administration (FDA) [FDA 2004]. In 2002 the FDA has formed a working group focussing on PAT. In order to encourage the voluntary development and implementation of PAT systems the guideline "Guidance for Industry PAT- A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance" was published by the FDA as a regulatory framework.

According to the definition of the agency, PAT is considered *"to be 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. It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical and risk analysis conducted in an integrated manner. The goal of PAT is to enhance understanding and control the manufacturing process which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design."* [www.fda.gov/Cder/OPS/PAT.htm].

A further goal of PAT is to understand the process entirely. In this context process understanding means the complete identification and explanation of all critical sources of variability. Furthermore, in a well understood process, an accurate and reliable prediction of product quality given attributes such as materials used, process parameters, manufacturing, environmental and other conditions is possible [www.fda.gov/Cder/OPS/PAT.htm].

The FDA's PAT approach has been selected on European level by the European Medicines Agency (EMEA) as well as by national agencies like the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in Germany. Both parties formed their own in-house PAT teams.

Furthermore, PAT's fundamental ideas are particularly implemented in ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines "ICH Q 8-Pharmaceutical Development" and "ICH Q 9-Quality Risk Management" [Hinz 2006].

Up until now there are multitude of tools available enabling and advancing process understanding (Table B-1).

Table B 2-1: *PAT tools [BfArM 2005]*

PAT tools	Application	Examples
Risk analysis	Registration of critical process parameter within knowledge space	FMEA (Failure Mode Effect Analysis)
Analyzing method	On-line, in-line or at-line measurements	NIR spectroscopy
DoE (Design of Experiments)	Analysis of influence of critical process parameter (analysis of effects and interactions), description of design space	Optimization strategy
MVA (Multivariate Data Analysis)	Prediction of properties of - raw materials - intermediate products - finished products - feed back to process control	PCA (Principal Component Analysis) PLS1 (Projection of Latent Structures)

It is important to know that the implementation of process analytical technology can not be achieved using only one isolated technology. In fact the combination of different tools is necessary to achieve the desired understanding of the process.

Finally, the PAT initiative follows the vision of achieving a real-time release by shifting the current downstream quality control into the production processes.

In this context the real-time measurement of critical process parameters gains more and more importance. It not only allows verification of product quality throughout the entire process but also improves process understanding.

The FDA’s PAT approach was the basis for the present research of this work. Within this study a new sensor system was developed and implemented in the manufacturing process of granules. By monitoring the granule moisture as an eminently critical process parameter in real-time the PAT approach should be fully met and process understanding should be improved for different medicinal products.

2 Granulation

In this study granulation processes, especially wet granulation processes, were investigated. This chapter provides a brief overview about granulation in general, and several manufacturing techniques.

2.1 General aspects

According to the definition of the European Pharmacopoeia granules are “preparations consisting of solid, dry aggregates of powder particles sufficiently resistant to withstand handling. They are intended for oral administration. Some are swallowed as such, some are chewed and some are dissolved or dispersed in water or another suitable liquid before being administered.” [Ph. Eur. 6.0].

Granules can be a self-contained dosage form. As such the European Pharmacopoeia distinguished between effervescent, coated, gastro-resistant and modified-release granules. The application of granules as a self-contained dosage form is not common practice. In fact granules are mainly intermediate products for the manufacturing of other dosage forms, usually tablets. Furthermore, granules can be used as filling material for capsules.

The granulation process itself is a process of particle enlargement [Serno 2007]. The increase in particle size is associated with a decreasing specific surface area as well as a reduction of the bulk volume. This should lead to an improvement of flow properties and metering accuracy. Furthermore, the plastic deformability is optimized as a prerequisite for compression. Further granule properties, such as wettability, porosity, solubility and disintegration time may also improve. It is also advantageous that demixing tendency and forming of dust is reduced by producing granules [Bauer 1999, Augsburger 1997].

2.2 Granulation processes

One possible classification of granules according to their manufacturing procedure is displayed in Figure B-1.

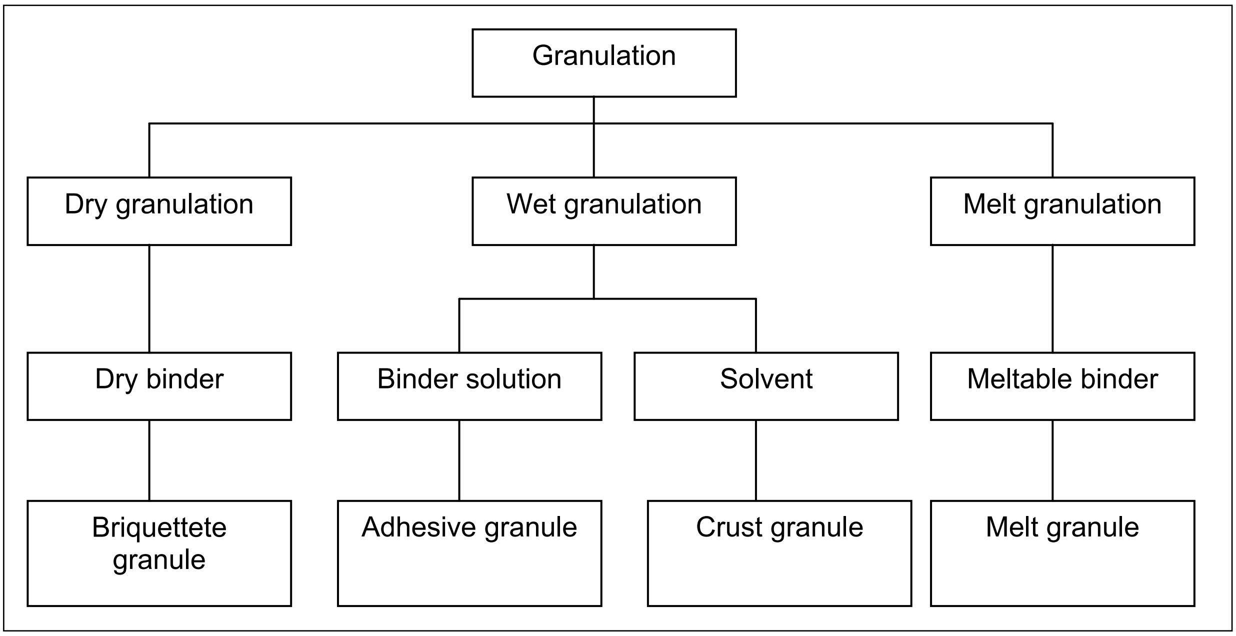

Fig. B-1: *Classification of granulation techniques [Serno 2007].*

Nowadays wet granulation can be regarded as the most common granulation technique. In wet granulation processes the agglomeration results from the use of an aqueous or organic solvent. The respective granulating fluid is removed by a subsequent drying step. Depending on the character of the granulating fluid two different granule types can be distinguished. By applying a binder solution adhesive granules are generated. Crust granules result from the usage of solvents, such as purified water or organic solvents.

By definition, wet granulation processes are constructive procedures as fine primary particles are built-up to coarser agglomerates.

During dry granulation processes, agglomerates, e.g. briquette granules, are formed by applying high mechanical pressure in combination with a dry binder. This technique is an example of degradation granulation processes where the finished granules are obtained from crushing bigger agglomerates.

Melt granulation demonstrates one further granulation technique. In this case meltable binders are used. With increasing temperature they are melted and subsequently solidify at ambient temperature. Consequently, the agglomeration of primary particles to bigger units is enabled and granule growth takes place.

2.3 Fluidized bed granulation

Wet granulation processes can be performed using different devices. Within this research the main focus was on wet granulation processes performed in fluidized bed apparatus.

At the beginning of a fluidized bed granulation process, dry raw materials are filled into the product container. By an air flow generated from ventilators a fluidized bed is build up with the solid material. In the following agglomeration of the fine primary particles is started applying the binder either per counter flow- or current flow principle. Subsequent to the spraying phase drying of the granules is performed until reaching the required residual granule water content.

While the process phases run in batch fluid bed systems consecutively, they proceed in continuous fluid bed systems parallel in several granulations zones within the process chamber. In the pharmaceutical industry the batch fluid concept bestride the processes of fluidized bed granulation [Leuenberger 2001].

Independent of the granulation process, granule properties are considerably influenced by their water content. Consequently, the moisture content should be rated and treated as an eminently critical process parameter, necessitating a tight control.

3 Moisture

In general the term “moisture” describes the presence of water in other gaseous, liquid or solid media. In this context the terms “product moisture” and “solid moisture” are deduced. For a more detailed characterisation, the umbrella term “moisture” can be specified as moisture content.

The moisture content (ψ) is defined as the amount of water in mass percentage, which is present in the material to be tested. The amount of water (m_w) can be related to the mass of the dry substance (m_d) (Eq. B-1) as well as to the total mass of the wet material ($m_d + m_w$) (Eq. B-2).

$$\psi = \frac{m_w}{m_d} \cdot 100 \ [\%] \qquad \text{(Eq. B-1)}$$

$$\psi = \frac{m_w}{m_d + m_w} \cdot 100 \ [\%] \qquad \text{(Eq. B-2)}$$

ψ *water content [%]*
m_w *mass of water [kg]*
m_d *mass of the dry substance [kg]*

For the determination of the water content numerous methods are available (see chapter B 4).

In the following course of this research the term “moisture” is used expressing the water content in relation to the total mass of the wet material.

3.1 Impact of moisture on pharmaceutical solid dosage forms

The water content of materials is a very important parameter in different industrial areas such as timber, food, tobacco or paper industry but also in chemical and pharmaceutical industry.

In pharmaceutical industry the sensitivity of the active pharmaceutical ingredient (API) and the excipients are co-determinative parameters for the selection of the appropriate formulation and manufacturing method during process design. For formulations containing a substance which is sensitive to hydrolysis, dry granulation would be preferred over a wet granulation. The water content of the raw materials to be used may also have a great influence on further processability as well as on product quality. This aspect is of critical importance for both, dry and wet granulation. In granulation processes fine granules result from dry materials due to their lower adhesive power [Serno 2007]. During wet granulation processes the product moisture is also an eminently important and critical parameter. According to Schæfer (1978) and Schinzinger (2005) high free water contents could lead to coarser granule particles. However, the granule moisture is not only a quality-determining parameter during granulation processes, but also for subsequent process steps and during storage. During compression crucial product properties e.g. hardness, friability, disintegration time, compaction force and speed are affected by the water content [Jong 1991, Faure 2001]. Poor residual granule water contents could cause insufficient mechanical resistance [Serno 2007]. An elevated residual moisture could have for example a negative influence on the stability of the dosage form or may cause insufficient disintegration or dissolution times.

Thus, moisture determination before, during and after pharmaceutical production processes becomes increasingly important. By performing directed moisture monitoring it is not only possible to influence product properties in a desired manner, but also to ensure product quality. Furthermore, it is possible to control the process e.g. to raise efficiency and reduce costs.

In order to achieve an effective moisture control the monitoring should be performed in real-time. An immediate response on the current water content and process variations is enabled.

Existing methods for moisture determination established in the pharmaceutical sector can be found in chapter B 4.

3.2 Binding types of water on solids

To determine the moisture content it is important to know that water molecules can be bound on solids in different ways. The type of water bound affects the properties of the material. Based on the different binding types a classification of the water-solid bindings can be carried out (Table B-2).

Table B-2: *Classifications of binding types of water on solids according to Bauer (1999)*

	Adhesive water	**Capillary water**		**Hydration water/ Swelling water**	**Adsorptive water**	**Hydrate water/ Crystal water**	**Constitution water**
		Rough capillary water	**Micro capillary water**				
Binding relation	continuous					discontinuous	
Mobility	free	free	decreasing			fixed	
Hydration heat [kJ/mol H_2O]	0	0	0-5	0-20	2-60	5-40	20-105
Examples	Wet solid surfaces	Glas frit	Silica gel	Gel, Gelatine	Hydrophilic solid surfaces	Crystal hydrates	Oxid hydrates

In order to characterize the water-solid bond the hydration heat [kJ/mol H_2O] is used, which is an indication for the strength of a bond. High values mean strong bonds, with a corresponding increase in the energy required to break an existing bond. Furthermore, the hydration heat allows a rating of the mobility of bounded water molecules with a low heat content referring to a free mobility of the water molecules.

With increasing hydration heat the mobility decreases until water molecules are immobile due to a particularly strong bond expressed by a high hydration heat.

Adhesive water is weakly bound on interfaces by electrostatic or van der Waals forces and can be eliminated easily.

Within **capillary water**, bindings are stronger depending on whether mainly rough or micro capillary water is present. Polar interactions are chiefly responsible for water-solid bonds for **hydration/swelling water** and for **adsorptive water**. Monomolecular layers are the most tightly bound and binding forces decrease with number of layers.

In **hydrate/ crystal-water** as well as **constitution water** water molecules are fixed in the crystal structure unable to interact with other free water molecules. Consequently, these bindings are extremely tight. Their separation and subsequent measurement is only possible under special conditions, e.g. by the destruction of the entire molecule.

Due to the fact that the different water bonds can coexist, and their proportion depends on the prevalent moisture, an accurate separation of the water bindings in solids is often difficult.

4 Methods of moisture determination on solids

As mentioned previously the moisture may have a great impact on the quality of pharmaceutical solid dosage forms. Therefore, continuous moisture control is of major importance.

In connection with the FDA’s PAT approach terms like “in-line”, “on-line”, “at-line” and “off-line” are often used to characterise an analysis technique. The term “in-line” describes a measuring system where the sample interface is located directly in the process stream. “On-line” stands for an automated sampling and transfer procedure to the automated analyzing equipment. The term “at-line” refers to manual sample withdrawal and transfer to the measurement equipment located in the manufacturing area. A manual sample withdrawal with subsequent transport to a remote or centralized laboratory is described by the term “off-line”.

Within this chapter, common methods for the determination of the water content, which are already applied in the pharmaceutical sector, are discussed.

Figure B-2 provides a summary of methods for material moisture measurement differentiating roughly between direct and indirect measuring methods.

Due to their respective measuring principle the different methods do not detect all types of water. Thus, the water binding type to be measured has to be considered for the selection of a suitable measuring method.

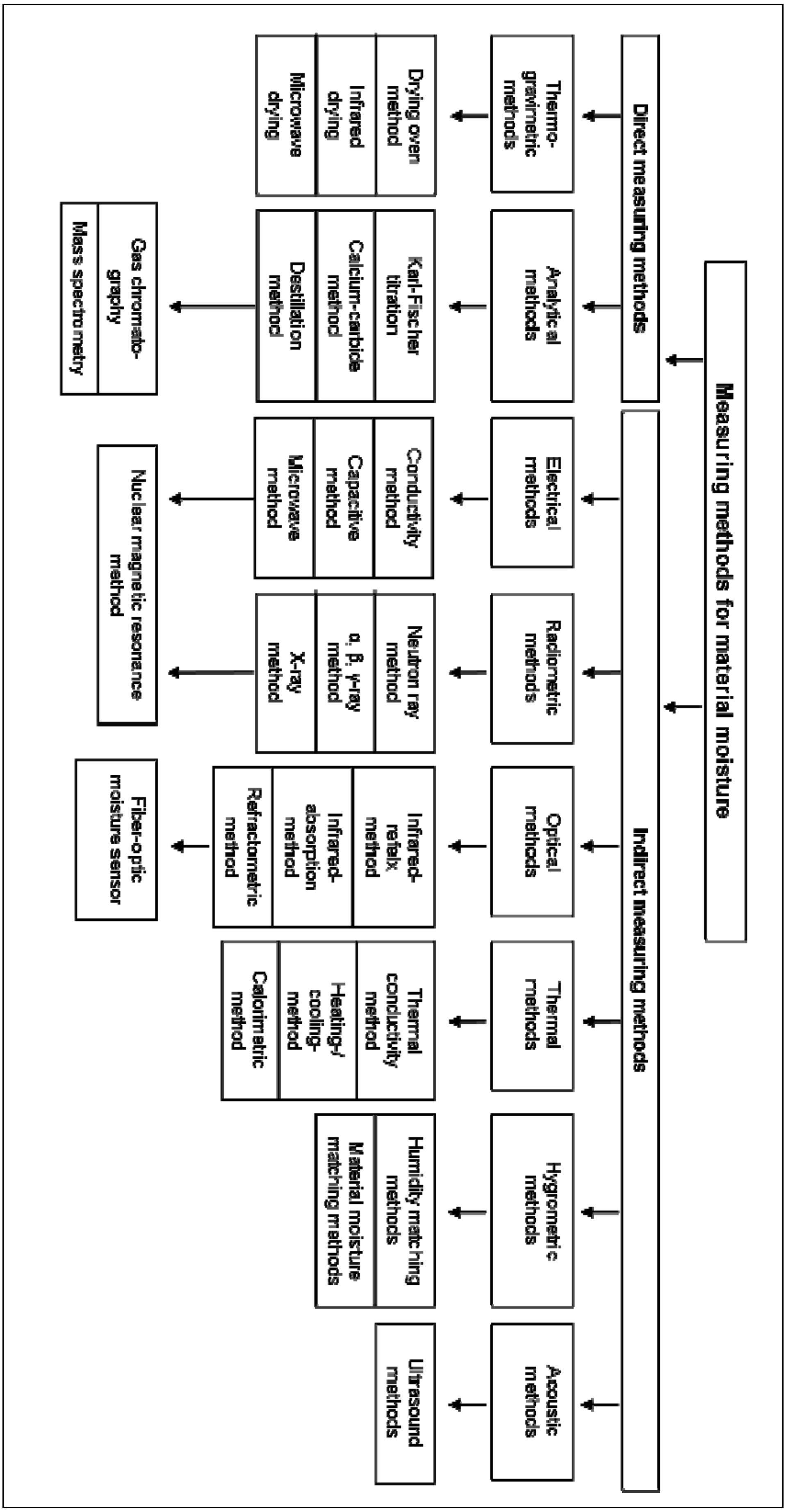

Figure B-2: *Summary of measuring methods for material moisture [Kupfer 2007.]*

In pharmaceutical technology mainly thermogravimetrical, analytical, such as wet-chemical methods (e.g. Karl Fischer titration) and optical (spectroscopic) techniques are used. The European Pharmacopoeia itemized in monograph 2.2.32 five methods for the determination of loss on drying. Karl Fischer titration is specified as semi-micro determination in monograph 2.5.12. IR and NIR methods are described in general, but not for moisture determination.

However, there are no specified reference methods for moisture determination or reference standards listed in the pharmacopoeias. Accordingly, the verification of the results of water determination is not possible. Due to the lack of a reference method, and the fact that the methods for water determination detect different water types, the identification and verification of a suitable method for moisture monitoring during granulation processes is quite challenging.

4.1 Direct measuring methods

Thermogravimetric methods: Drying oven and heat balance

The basic principle of all gravimetric measuring methods is identical: the direct determination of the loss on drying (LOD) is carried out. Due to external heat supply the water fraction of the substance to be investigated gets evaporated. Performing a differential weighing of the initial raw body mass (m_0) to the mass after the measuring interval (m_t) loss on drying gets determined as mass loss in percentage (Equation B-3).

$$\text{LOD} = \frac{m_0 - m_t}{m_0} \cdot 100 \; [\%] \qquad \text{(Eq. B-3)}$$

LOD *loss on drying [%]*
m_0 *mass of the initial raw body [kg]*
m_t *mass after the measuring interval [kg]*

Several gravimetric methods for moisture determination exist, which differ in technical setup, measuring time and in the type of the energy supply required for evaporation of water.

The advantages of the determination of the loss on drying are low technical complexity and the simple implementation. However, the main disadvantage is that this method does not allow the separation of water and other nonaqueous solvents respectively volatile substances. In addition, weighing of samples is a potential source of error. Uplift pressures in the hot sample material may distort the measurement. However, cooling of the sample prior to weighing could lead to re-absorption of water molecules resulting in incorrect results.

The most often used equipment for the determination of the loss on drying is the drying oven. A defined mass of the sample is inserted into the drying oven and dried for a predefined period or until constancy of mass, both at a predefined temperature. Afterwards the sample material is measured once again, and the loss on drying calculated using equation B-3.

Performing this method requires several hours, and therefore this method is not suitable as an in-line measuring tool. Its application as an off-line reference method during production is also limited, as a rapid measurement of in-process data is required in order to ensure a real-time response.

One further gravimetrical apparatus for the determination of the loss on drying is the heat balance. The measuring principle is the same as the drying oven. Within this device the balance and heating element are directly combined, which, along with automated measuring, results in facilitated handling for the operator. The measurement can be performed at various temperatures over a predefined time, or until a constant mass is achieved. A specific measuring jacket is uniformly filled with the material to be investigated and the measurement is started. Measuring control, as well as the calculation of the results as a loss of mass in percentage, is performed automatically.

The main radiation sources used for the heat balance approach are infrared, halogen and microwave generators. By using infrared radiation (IR) as a heat source, two main disadvantages occur. IR radiation only has a low penetration depth, so that only the water molecules on the material’s surface are detected. Water located deeper in the material can not be determined. Furthermore, the heating of the material proceeds from outside to inside. Due to fouling, there is a risk of waterproof coating emerging. This coating may constrain the evaporation of water.

The use of halogen bulbs as a heat source, results in a considerably more effective heat expansion resulting in shorter analysis times.

As microwave radiation permeates the entire material, heating of the sample takes place from inside to outside. The moisture of the complete material is determined. Furthermore, the risk of fouling decreases.

As the application of all three types of energy described above is more effective than in the drying oven, the measuring time is shortened considerably.

Due to the very simple technique and rapid measurement, heating balances are well established for moisture determination. Heat balances are often used as an off-line measuring tool for the determination of the drying endpoint of wet granulation processes.

Analytical methods: Karl Fischer titration

Karl Fischer titration (KF) is a well-established method for the quantitative determination of water content via iodometric titration. It depends on the reduction of iodine by sulphur dioxide, which proceeds only in presence of water. Thus, water is determined as a stoichiometrical reactant.

An anhydrous alcoholic solution (usually anhydrous methanol) is used as a solvent. Furthermore, the presence of a base with adequate buffer capacity, e.g. pyridine, is required.

In the first step of the reaction (Equation B-4) sulphur dioxide (SO_2) reacts with alcohol, in this case anhydrous methanol (CH_3OH), an acidic ester, which is neutralized by the alkaline component (RN).

$$CH_3OH + SO_2 + RN \longrightarrow [RNH]SO_3CH_3 \qquad \text{(Eq. B-4)}$$

Monomethylsulfite, the adduct of the first step of reaction, is oxygenated to monomethylsulphate in the presence of water and iodine (Equation B-5). Thereby iodine is deoxidized to iodide with stoichiometrical consumption of water.

$$H_2O + I_2 + [RNH]SO_3CH_3 + 2RN \longrightarrow [RNH]SO_4CH_3 + 2[RNH]I \qquad \text{(Eq. B-5)}$$

By this reaction mechanism, an almost selective determination of the water content becomes possible. However, potent deoxygenizing, strongly acidic or alkaline substances as well as ketones or aldehydes may interfere. Determination of the endpoint can be performed visually or, in accordance to Ph. Eur. monograph 2.5.12 “Water: Semi-micro Determination”, electrometrically.

In cases of substances/ products being insoluble in methanol, a special form of Karl Fischer titration enables the water determination. The material to be measured is heated, and the water removed is transported to the measuring cell, via nitrogen flow.

The European Pharmacopoeia specified the coulometric Karl Fischer titration as well. When applying this method, the iodine required is not added externally, but generated by anodization from existing iodide in the solution. In the following run, iodine reacts directly with the water to be determined. During the titration only iodide is freely available in the solution. However, at the end of the reaction, both iodine and iodide coexist, providing a reversible redox couple. This causes a current flow which enables the determination of the endpoint [Peters 2007]. On the basis of the current consumption for anodization of iodide, the water content of the sample can be calculated. Using this special form of Karl Fischer titration, even very low water contents can be measured.

Independent of the method of endpoint determination, Karl Fischer titration enables the measurement of both physically and crystallographically bound water.

Two key advantages of this direct method are the automation of the analyzing process and the high sensitivity. However, the toxicity of Karl Fischer reagents, and the formidable complexity of sample preparation are limiting aspects for the application of Karl Fischer titration as a reference method during production processes.

For process control usually only the proportion of physically bound water (e.g. adhesive water) is considered, as it affects product properties during and after the process in particular. If the respective product contains e.g. crystal-water, its amount has to be subtracted from the original KF results. This procedure is quite challenging and due to the resulting great risk of errors a further limiting aspect for the application of KF, especially for pseudopolymorphs, whose crystals may contain varying amounts of crystallographically bound water.

4.2 Indirect measuring methods

Electrical methods: Microwave and nuclear magnetic resonance

The microwave method enables an extremely fast, non-destructive and contact-free moisture measurement. Using this method an electromagnetic field is induced by microwave radiation with frequencies from 300 MHz to 300 GHz, according to wavelength ranges from 1 mm to 1 m. Amongst other parameters, the high dielectric constant of water molecules is used for the selective determination of the water content (see chapter B 5).

Within first attempts, microwave spectroscopy was used as a one parameter measurement for in-line moisture determination during fluidized bed granulation processes [Glatt GmbH EP 0970369B1 1997]. As this method depends on product density, its application for moisture determination in fluidized bed processes is limited (see chapter B 5).

Using nuclear magnetic resonance spectroscopy (NMR) the behaviour of atomic nuclei is observed. Commonly, it is used for structure determination of complex molecules and enables the characterization of intra- and intermolecular interactions and molecular dynamics [Wolter 2005]. Besides providing chemical and physical information, NMR spectroscopy is often applied, for example in the food industry for the determination of the water content of starch, seeds and potatoes [Brosio 1978, Kuhn 1986].

NMR spectroscopy is based on the measurement of absorption of electromagnetic radiation in the high-frequency range from 4 MHz to 600 MHz.

A precondition for the application of this non-destructive analyzing method is an odd nucleon number of the substance to be investigated, as these atomic nuclei feature nuclear spin and thus a permanent magnetic moment.

For the determination of water content ^{1}H NMR spectroscopy is well known. The measurement is based on the fact that the protons of hydrogen atoms interact with the applied electromagnetic field. Due to the rotations of the hydrogen atoms contained in water molecules, it is possible to induce a current in a coil. This current is directly proportional to the volumetric water content [Wernecke 2003].

Due to the great financial and technical complexity, this method is not available as an in-line reference method during production processes. For the same reason NMR spectroscopy is only rarely used as an off-line reference method for water determination. In the pharmaceutical industry NMR spectroscopy is for example used for the detection of polymorphism in pharmaceuticals.

Vibrational spectroscopic methods: near-infrared and infrared spectroscopy

Vibrational spectroscopic methods such as near-infrared (NIR) as well as infrared (IR) spectroscopy are based on the same principle. IR wavelength range from 780 to 100,000 nm and NIR wavelength range from from 780 to 3000 nm. In particular, the frequency range of NIR radiation is used for the determination of water content.

The Raman spectroscopy is one further vibrational spectroscopic method. As it provides no specific water bands, it is not used for the determination of the water content. In contrast, Raman spectroscopy is well established for various applications such as the structure determination of chemical substances and as PAT tool in film coating [El Hagrasy 2006, Müller 2009]

The vibrational spectrocopic technique involves inducing an electromagnetic field. This initiates vibrations of slightly bounded water molecules. The energy required gets disposed from the electromagnetic field.

The loss of energy is proportional to the number of water molecules in the material. The wavelengths used considerably affect the selectivity of the measurement. Particularly strong absorptions of water molecules can be found at specific frequencies (e.g. 1450 and 1940 nm) [Brokmann 1997]. Consequently, the characteristic water bands in the spectra of the frequency range are well suited for the determination of the water content.

In principle two methods can be distinguished: reflectance and transmission spectroscopy. Both techniques are based on infrared absorption by the measured material [Brokmann 1997].

As both NIR and IR spectroscopy are indirect measuring methods, a calibration against a direct moisture measuring method is required. Due to substance specific binding relations, calibration is required for each substance and each composition. This results in a relatively complex calibration process.

Due to being contact-free, non-destructive and providing a rapid response, NIR spectroscopy enjoys great popularity for moisture determination. However, product related properties, e.g. graining or colour, could interfere.

In the pharmaceutical industry, NIR spectroscopy is a well-established method in various areas, e.g. for assay and content uniformity testing of tablets [Merckle 1998, Trafford 1999] or for evaluating the efficiency of film coating processes [Buchanan 1996]. Goebel (1998) reported that on-line spectroscopy was used within fluidized bed granulation processes for the determination of moisture and particle size. Furthermore, near-infrared spectroscopy provides the ability to monitor the moisture content during other processes, such as microwave vaccum drying [White 1994] or hard gelatin capsule manufacturing [Berntsson 1997].

In order to control fluidized bed granulation processes by in-line moisture monitoring, there have been several attempts to make use of NIR spectroscopy [Methfessel 2006, Mattes 2005, Rantanen 2001, Wildfong 2002].

For example, the application of an infrared moisture analyzer was reported by Watano (1991, 1994, 1996) for the in-line monitoring of granule water content, feedback control and process control in an agitation fluid bed granulator. However, the low penetration depth of IR radiation could have a negative influence on measuring accuracy, due to the redistribution of water molecules that occurs, which depends on dampening speed [Watano 1996].

As previously mentioned both NIR and IR have low penetration depths due to their short wavelength and resulting high levels of reflection. This implicates that only the moisture content on the product's surface can be detected. Furthermore, NIR and IR absorption depends strongly on the total number of measured particle layers and the powder density of the solid material. Besides this product fouling on the measuring window turns out to be problematic due to increased reflections of the radiation, and resulting in unreliable moisture measurement [Glatt GmbH 1997]. First technical approaches are available to overcome the problem of fouled measuring windows. For example, an NIR measuring system providing a self-cleaning window, to be mounted in the granulator's container wall has been developed [NDC 2007].

Using a similar basic principle, a new probe technique is also available where the NIR probe extends into the product space of the fluidized bed. In this case the measuring window for NIR measurement is directly implemented onto the probe, and can be cleaned during an ongoing process by a self-cleaning system [Mannhardt 2007].

Both methods provide sophisticated approaches, however new critical issues emerge, for example the measuring window is in contact with cleaning agents during ongoing processes and the measurement is interrupted throughout cleaning time, and should be taken into consideration.

As can be seen in this chapter, various methods for the determination of the product moisture are available. However, up until now, there is no method available without remarkable limitations that allows the determination of granule water content in fluidized bed processes in real-time. Therefore, the aim of this study was to identify a suitable measuring method that enables the determination of granule water content during fluidized bed granulation in real-time with sufficient accuracy and precision.

5 Microwave resonance technology as in-line measurement tool

Compared to the methods described above, moisture measurement by microwave resonance technology has hardly been used in the pharmaceutical sector. However, in a multitude of industrial sectors it is used successfully.

Off-line measurement- as well as in-line measurement techniques are implemented in various processes. Börste (2007) and Döscher (2007) described the application of microwave resonators for the optimization of moisture and process control during manufacturing of medium density fiberboards. Furthermore, microwave resonance technology is reported for determination of residual moisture within production processes of parquet and solid wood components [Holzkurier 2006]. Also in production processes of animal feed, microwave resonance sensors are implemented into the process flow in order to obtain a real-time moisture determination [Johnson 2007].

The technique has also been employed in the filling process of coffee [Daschner 2006] and tobacco industry [Tabacco Journal 2002].

Melichar described in 2007 first approaches of using this technique in the pharmaceutical industry. However, in this case the microwave resonance sensor system was used as off-line tool for moisture determination and not as in-line method for real-time process control.

5.1 Measuring principle

The determination of the water content of solid materials is based on the interaction between water molecules and changing electromagnetic fields, induced by microwave radiation.

Due to the strongly differing electronegativity of oxygen and hydrogen atoms within the water molecule and their angulated configuration (see Figure B-3) a permanent dipole moment of 1.844 Debye is produced.

One further characteristic variable of water molecules is the dielectric permittivity, with a value of 80.35 (20°C), which exceeds other substances considerably.

Based on these remarkable characteristics, a nearly selective determination of the amount of water molecules is possible using microwave resonance technology.

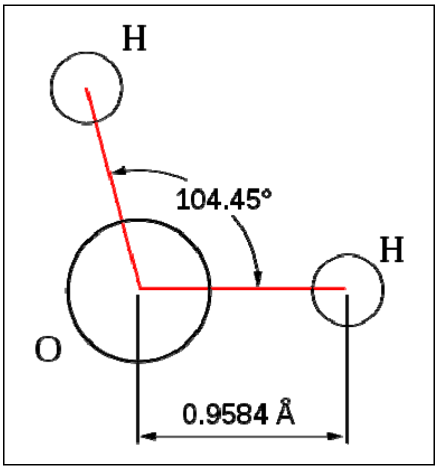

***Fig. B-3**: Angulated configuration of the water molecule*

Without external stimulation, water molecules, as dipoles, are disordered within the solid particles (Figure B-4 A). By inducing an electromagnetic field with alternating polarity via microwave radiation, dipole molecules became aligned according to the polarity of the field (orientation polarisation) (Figure B-4 B).

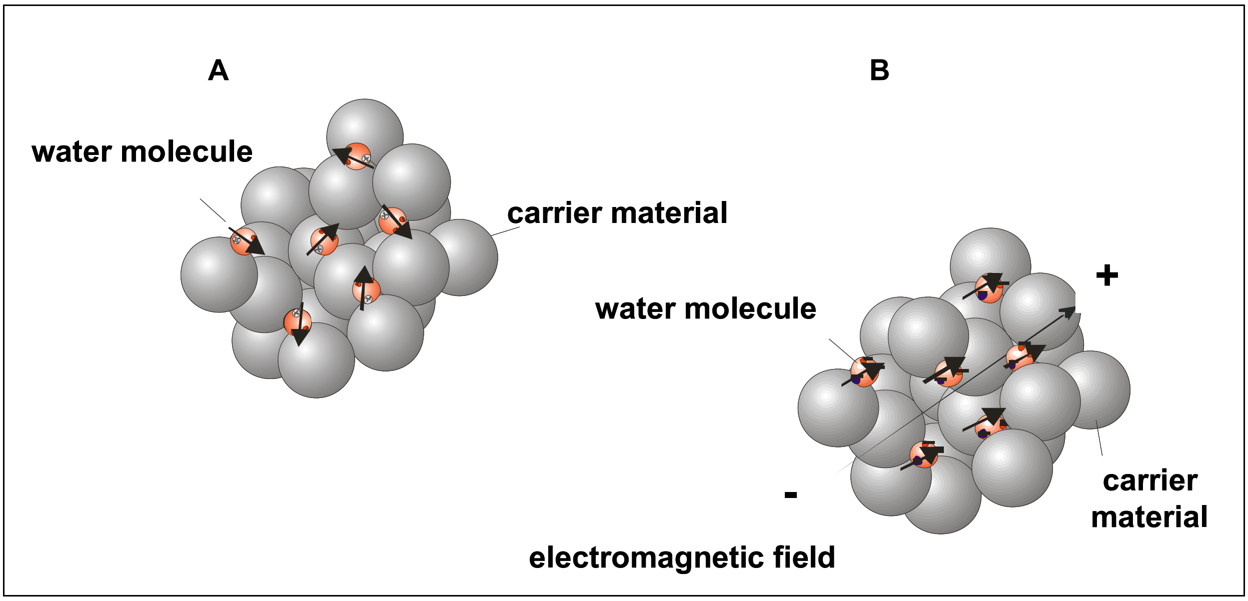

Fig. B-4: *Alignment of water molecules without (A) an electromagnetic field and after external stimulation. (With kind authorization from AMS Advanced Microwave Systems GmbH.)*

The higher the frequency and the larger the dipole moment the faster the alignment of the molecules occurs. However, this procedure is limited by a maximum frequency. Further increase of the frequency results in the inability of the water molecules to follow the electromagnetic field; dipole relaxation frequency is reached. For water this frequency is about 20 GHz. When exceeding this frequency a phase shift results between the polarisation of molecules and the electromagnetic field leading to a decreasing dielectric permittivity. This relation is expressed by Equation B-6 [Kupfer 1997]:

$$\varepsilon_r = \varepsilon'_r - j \cdot \varepsilon''_r \qquad \text{(Eq. B-6)}$$

ε_r	*relative dielectric permittivity*
ε'_r	*real part*
j	*imaginary unit*
ε''_r	*imaginary part*

The real part ε'_r describes the polarizability and the imaginary part ε''_r characterizes the phase shift between polarisation of molecules and the electromagnetic field. Both ε'_r and ε''_r depend on frequency, as shown in Figure B-5, as well as on temperature and material density.
As seen in Figure B-5, a lower limitation of the measuring frequency of approximately 10^{-3} GHz exists due to ionic interactions disturbing the measurement.

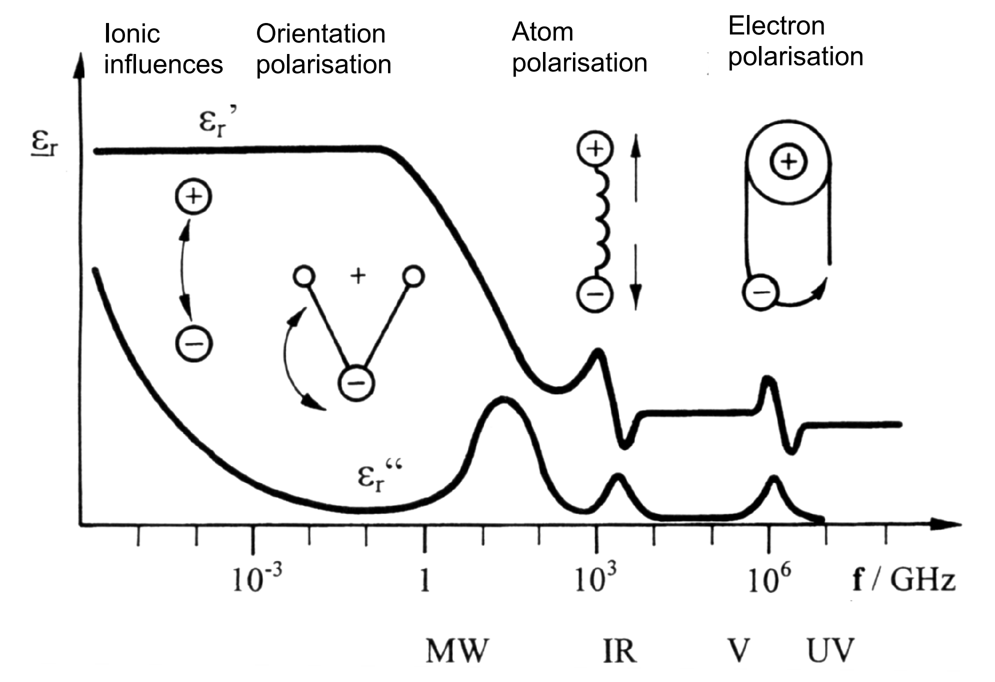

Fig. B-5: *Spectral distribution of polarisation effects [Kupfer 1997].*

For each flip of the water molecules due to the alternating electromagnetic field, a loss of energy that is disposed from the field can be determined. This results in an increasing width of the resonance waves. Furthermore, the resonance frequency decreases simultaneously in comparison to the unstressed sensor (see Figure B-6). The energy disposed correlates with the total number of water molecules in the medium [Döscher 2002].

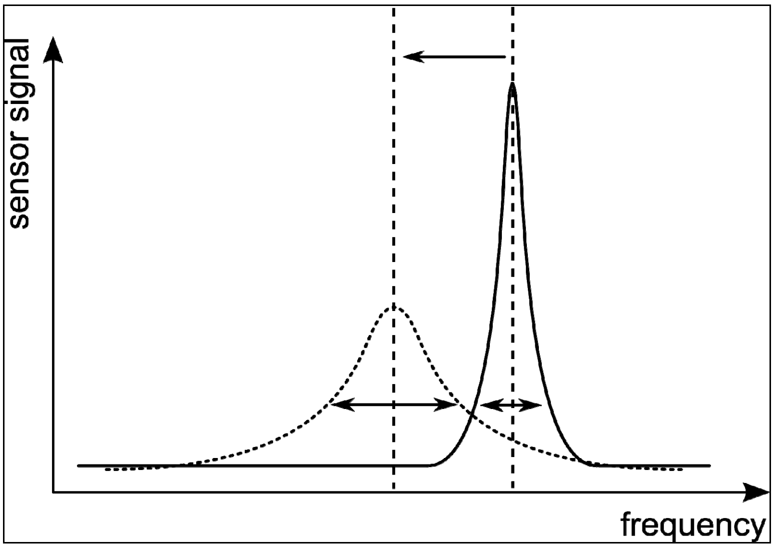

Fig. B-6*: Microwave resonance curves of the unstressed and loaded sensors. The microwave resonance frequency decreases with increasing water burden, while the frequency bandwidth becomes broader. (—) Resonance curve in air (unstressed sensor), (·····) resonance curve in wet material (loaded sensor) [Buschmüller 2008].*

The total amount of water measured in the sample does not give an appropriate indication of the water content in the solid material, as the signal does not reflect the powder density. By performing this one parameter measurement, only the broadening of the frequency bandwidth respectively the loss of energy is evaluated. Consequently, the results are affected by particle density. Therefore, it is a precondition to keep density and layer thickness constant in order to minimize their influence. For off-line laboratory devices this may be possible or may be provided by model assumptions, but for in-line measurement of moisture during production processes, the density independency of the signal must be assured. Especially in fluidized bed processes with varying powder densities, the independence of the method for water determination from the material density is required.

In order to compensate the influence of density, various approaches were considered. For example systems were built which mold the sample in a predefined manner. Thus, the bulk density and layer thickness of the sample are kept constant [Kalinski 1979, Kalinski 1984]. Later on, different methods were combined to obtain a density corrected moisture value. Thus, Klein revised microwave values using gamma radiation to determine particle density [Klein 1978].

Although these approaches have the right direction, they are associated with their intrinsic disadvantages. Systems for molding samples are often more complex and interference-prone than the device for moisture determination itself [Kupfer 1997]. By combining several methods for moisture and density measurement, their specific failures may be enhanced multiplied.

Melichar (2007) characterized first approaches to use the one parameter technique in the pharmaceutical sector. He focused on the determination of moisture content of powder and granules using a lab device for off-line measurement. A reproducible filling of the sample container was found to be a precondition to minimize influences of product density.

Furthermore, the company Glatt reported in 1997 about first attempts to make use of the one parameter technique for moisture control of fluidized bed processes. However, dependency on product density of the measurement caused an unreliable moisture determination.

In this context, a two parameter measurement offers the possibility to perform a density independent moisture measurement without having the disadvantages described above. As mentioned previously, an increasing water burden leads to a simultaneous decrease in resonance frequency and increase of frequency bandwidth (Figure B-6). Both parameters are determined simultaneously. By comparing both parameters to the unstressed sensor in air, two independent properties become available. This enables the determination of two product attributes, the moisture and the density. A density independent moisture determination, and vice versa, a moisture independent density measurement can be achieved.

In order to obtain reliable results, the previous measurement of the unstressed sensor is required.

As described above, the frequency bandwidth (B_E) as well as maxima of resonance frequency (f_E) of the sensor in air are measured. During the following wet materials measurement, the decrease of the resonance frequency (Δf) and the broadening of the bandwidth (ΔB), depend on the product density, but to a different dimension on the water content (Ψ). The calculation of the ratio of bandwidth magnification and the decrease of resonance frequency eliminates the influence of solid particle density (Equation B-7):

$$\psi = \frac{\Delta B}{\Delta f} = \frac{B_F - B_E}{f_E - f_F} \qquad \text{(Eq. B-7)}$$

Ψ	*water content*
ΔB	*difference of bandwidth [Hz]*
Δf	*difference of resonance frequency [Hz]*
B_F	*bandwidth of the loaded sensor [Hz]*
B_E	*bandwidth of the unstressed sensor [Hz]*
f_E	*resonance frequency of the unstressed sensor [Hz]*
f_F	*resonance frequency of the loaded sensor [Hz]*

Thus, the moisture function (M(Ψ)) is only a function of the moisture content, and the moisture content and product density can be determined independently [Knöchel 2007].

Figure B-7 demonstrates how the density dependence of MRT moisture measurement is eliminated due to a two parameter measurement. In this graph the loss of energy (dE, damping) is plotted against frequency shift (dF) of one material with two different moisture contents, resulting in two lines through the origin with different slopes. The black line demonstrates a material with low water content and the grey line the same material with high water content. For each resulting line through the origin, and therefore for each moisture content of the material, the characteristic angle α can be determined.

Each data point on the black, or respectively on the grey line corresponds to a particular test interval with identical moisture but varying density. Thereby, an increasing material density leads to increasing frequency shift (dF). As described previously the loss of energy and the frequency shift depend on the product density, but to a different dimension on the water content. By calculating the ratio of both detected parameters, the impact of the density is eliminated. Consequently, the angle α is characteristic for a particular moisture content, and independent from product density. It can be determined from each data point of the respective line through the origin.
From the angle α the microwave value (MW) is generated. Using the respective software the moisture content [%] is calculated from the microwave value.

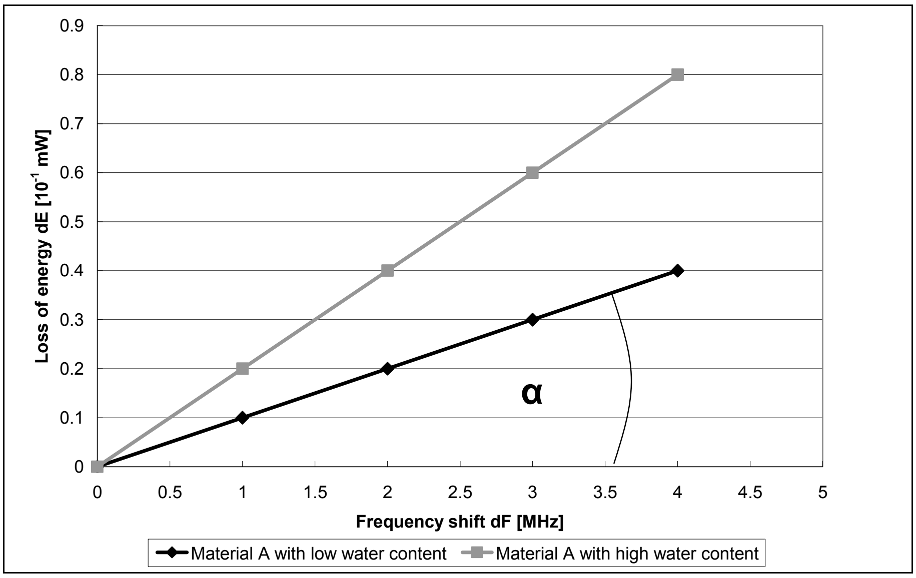

Fig. B-7: *Density independence of moisture measurement due to a two parameter determination.*

5.2 Configurations of microwave resonators

According to the purpose and site of the measuring device, multitudes of configurations are available. For off-line determination of the water content of individual samples using laboratory equipment, different requirements are necessary than for sensor systems that are implemented inside manufacturing equipment for in-line measurement of moving bulk solids.

For lab measurements using microwave resonance technology **cavity resonators**, as closed resonator, are typically used (for example in the coffee industry). The inner walls are constructed in a way that a low-loss reflection of incoming electromagnetic waves inside the cavity is possible. Thus an electromagnetic field results with a defined sensitivity. The material to be measured is now guided through this area directly and the moisture is determined.

However, often the test materials and process management does not permit the guidance of samples through such a cavity. Consequently, and of increasing importance for in-line moisture measurement during on-going processes, other tools are needed.

In such cases **stray field resonators** are particularly suitable, for example for moisture determination of animal feed in silos. Stray field resonators represent open resonators with an external electric stray field which extends into the product space. The resonator consists of, for example, a ceramic circular waveguide composed of aluminium oxide embedded in a stainless steel disc (Figure B-8).

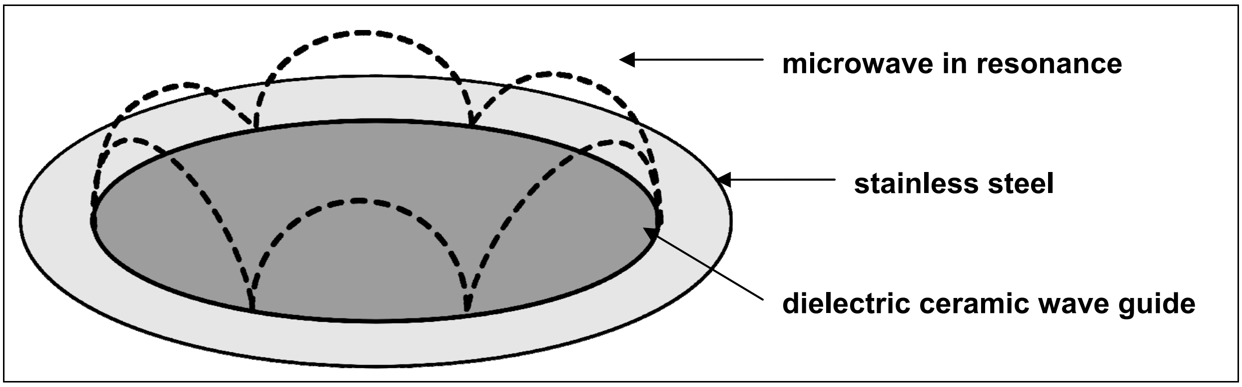

Fig. B-8: *Principal set-up of a stray field resonator.*

Inside the waveguide resonances are stimulated in such a manner that the perimeter of the loop corresponds to full multiples of the wavelength. Accordingly, several resonance frequencies are available from which usually only one is evaluated [Daschner 2006]. As noted above the stray field extends into the product space. By inserting wet materials over the sensor's surface into the standing electromagnetic field the resonator undergoes changes as described before (Figure B-9 A and B). The herewith accompanying distance-less measurement results in increasing metering precision.
In order to obtain complete compensation of environmental influences and other interacting variables, an independent reference unit was incorporated in the sensor (Figure B-9 C).Thus, improved precision and repeatability is assured [Knöchel 2003]. Using this type of configuration the in-line moisture monitoring of moving bulk solids is enabled.

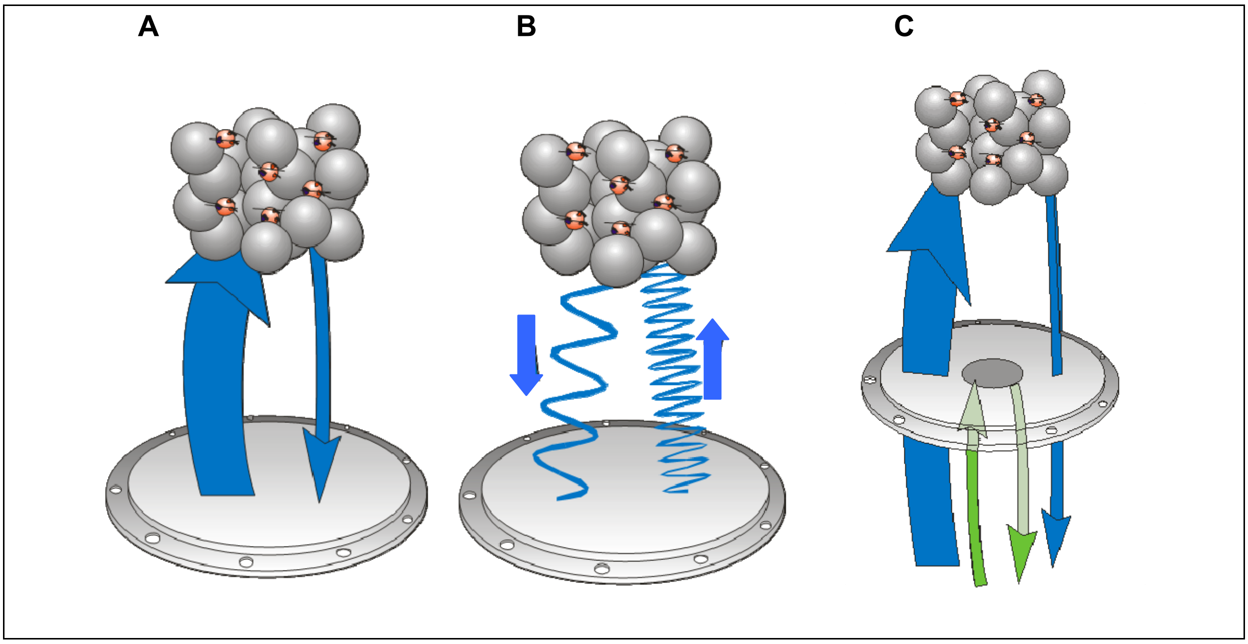

Fig. B-9*: Principle of moisture determination by microwave resonance technology. Absorption of microwaves by water molecules (A). Frequency shift of microwaves by particulates (B). Correlation of the signal to a reference sensor in the center (C) (EP 1331476). (With kind authorization from AMS Advanced Microwave Systems GmbH.)*

For microwave resonance sensor systems used within pharmaceutical processes unique requirements have to be met. More detailed information about the specific requirements on the sensor system developed and used within this research can be found in chapter C 1.

5.3 Basic elements of measuring system for in-line moisture monitoring

In a computer-controlled **generator** microwaves ranging from 2 to 3 GHz are excited. Their output power is between 10 µW and 10 mW. This is sufficient for tripping dielectric effects but dielectric heating does not occur. The fact that samples are not heated up is very important for the pharmaceutical industry, as heating of the product may for example lead to instabilities of the API. The **resonator**, in this case a stray field resonator, is supplied with induced microwaves over a **coax cable**. The coax cable is shielded so that microwave radiation cannot be radiated into environment and a nearly lossless transmission to the resonator is assured.

The frequency excited by the generator is selected so that inside of the resonator a standing electromagnetic field is generated. However, the frequency is not maintained at one predefined frequency, but it can be moved within the range of resonance.

Coupling of the microwave signals to the analyzer takes place using a coax cable as well. The **interfaces** of the sensor system are connected to a **computer**, which controls both the measurement and the evaluation of the microwave signals. Using the associated **software** a respective moisture value is determined and displayed in real-time.

Furthermore, a graphical evaluation of the measuring run and incorporation of reference values is possible. Directly below the senor's surface a PT 100 thermo sensor is installed, with its electric resistance dependant on temperature. Consequently, temperature can be determined as a further measurand in real-time.

It can be concluded that in the beginning of the present studies, there was no method available that meets the demands of a density independent in-line water measurement in pharmaceutical processes.

Microwave resonance technology seemed to be a promising tool for in-line moisture determination, but has not been applied to fluidized bed processes yet.

Within the present work the main focus was on enabling the usage of the two parameter microwave resonance technique in pharmaceutical fluidized bed processes in order to obtain a reliable real-time moisture control independent from the product density and to evaluate the signals provided by the measuring tools.

As the APIs used within this work are very sensitive to high moisture contents, a real-time control of the moisture is of particular importance to ensure product quality.

C Results and discussion

1 Microwave resonance sensor system for pharmaceutical application

So far only a few technologies such as NIR and IR spectroscopy allow the determination of residual granule water content in fluidized bed processes. However, these methods are associated with considerable disadvantages for reliable moisture determination of moving solids, as both techniques depend on product density. One further crucial problem is the sensitivity of the measuring system to fouling. Small quantities of product sediment can affect the measurement severely. Further limiting factors include sensitivity to coloured products and low penetration depth of the radiation. Therefore, it was of major interest to implement a novel measuring principle, which is not associated with such restricting disadvantages, in pharmaceutical fluidized bed processes. Microwave resonance technology was chosen as a suitable measuring method.

Up until now there was no suitable microwave resonance sensor system available for in-line application in pharmaceutical production processes, even though this technology has already been applied to other industrial sectors. However, the implementation to pharmaceutical production processes comes along with particular requirements. The process to be investigated within this study, namely manufacturing of wet granules in fluidized bed granulators, is associated with complex demands on measurement equipment. Fluidized bed processes can be regarded as worst case scenario, as varying powder densities and moisture contents occur within the process.

In order to introduce this technology in the pharmaceutical sector, numerous basic considerations had to be made on construction as well as on the measuring technique itself.

The following chapters focus on these specific requirements and on the implementation of a suitable sensor system in two different fluidized bed apparatus.

1.1 Sensor construction

According to the requirements of current GMP guidelines special demands on construction- and installation materials, in particular on materials intended to get into direct contact with the product, have to be met in order to avoid undesirable interactions [cGMP guidelines]. For instance, the contact between granules and aluminium surfaces could lead to a discoloration of the solid particles [Bender 2007]. Metal ions may catalyze the degradation of active ingredients and excipients.

Due to the fact that the sensor system is in direct contact with the product throughout the entire process, special requirements concerning the materials used have to be met. Therefore, the former sensor construction was revised. Figure C-1 A shows the conventional stray field resonator construction as it is used for moisture determination, for example in the timber industry. The sensor setup developed within the present studies for pharmaceutical use is shown in Figure C-1 B.

Titanium replaces stainless steel in the base plate of the sensor head, as it is extremely resistant against abrasion forces and eluting. In addition the ceramic disc was replaced with a disc made from titanium and the dielectric ceramic wave guide is embedded directly into the titanium without adhesives which may elute substances into the product material. In comparison, the conventional sensor consists of the dielectric wave guide located under the ceramic disc, held together by a layer of two-component adhesive.

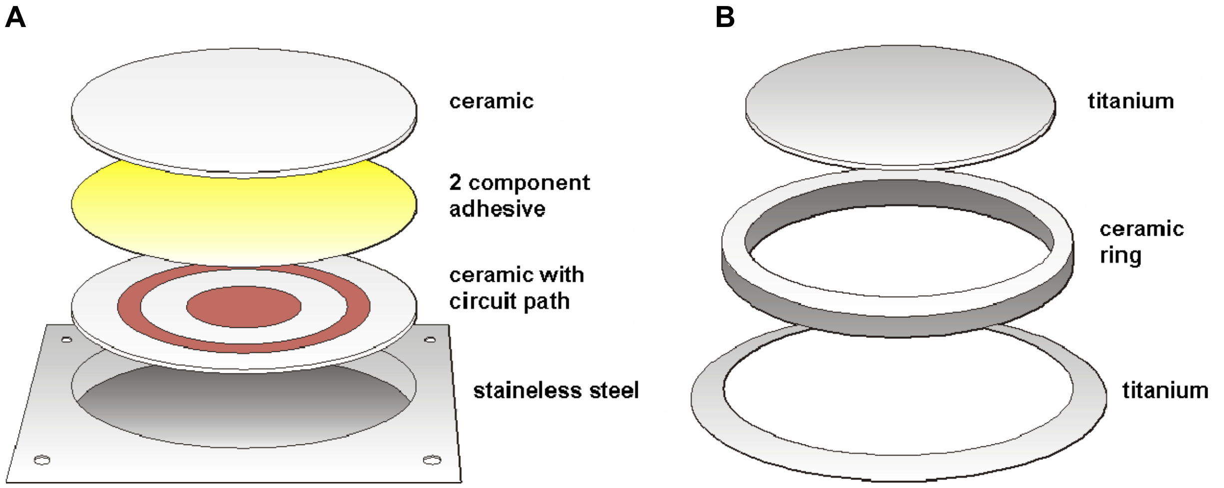

Fig. C-1: *Construction of microwave stray field resonance sensor head with conventional (A) and revised (B) setup (EP 1437588). (With kind authorization from AMS Advanced Microwave Systems GmbH)*

The sensor side of the measuring system is additionally equipped with dust explosion control. Due to implementation in fluidized bed granulators, the sensor system is compression-prooven up to 15 bar.

The novel sensor system hydorpharm fbma® was developed within the present studies in collaboration with the company AMS Advanced Microwave Systems GmbH.

1.2 Mounting

Additionally to the requirements on sensor components, numerous aspects concerning positioning of the sensor had to be considered prior to mounting on both fluidized bed granulators, WSG 60 and GPCG 15. The mounting position of the sensor system had to ensure a representative moisture measurement throughout the entire granulation process. In order to obtain a reliable determination of granule water content, there must be a continuous product flow above sensor’s surface. Simultaneously, it had to be assured that the mounting position has no negative influences on the product flow pattern.

Consequently, it was required to install the sensor head flush to the wall of the product container. Therefore, the curvature of the product container, varying depending on mounting height, had to be taken into consideration for sensor head construction as well. Complicating construction, both granulators are of different sizes. The WSG 60 features a capacity of 60 kg per batch, while GPCG 15 has a capacity of approximately 18 kg. To have a common sensor head, the design must be independent from the granulator capacity.

One further important aspect for defining the mounting position is that the positioning must guarantee that no cracks or clearing exist, which may cause fouling of the product. In this context the requirement of the GMP guidelines of avoiding the risk of cross contamination are important. Furthermore, residues of fouling products may affect a proper and correct measurement. Therefore a reliable, easy and reproducible cleaning of the sensor system and the granulator must be ensured.

For both types of granulators, the section of the lower third part of the product container was identified as the most suitable section for mounting the sensor system (see Figure C-2 and C-3). Within this area it is possible to meet all the requirements described above. Furthermore the sensor is installed at the same height as the sample probe already integrated in the granulators (Figure C-4). Thus, comparison of the results of moisture determination between microwave resonance technology and the reference method used is possible.

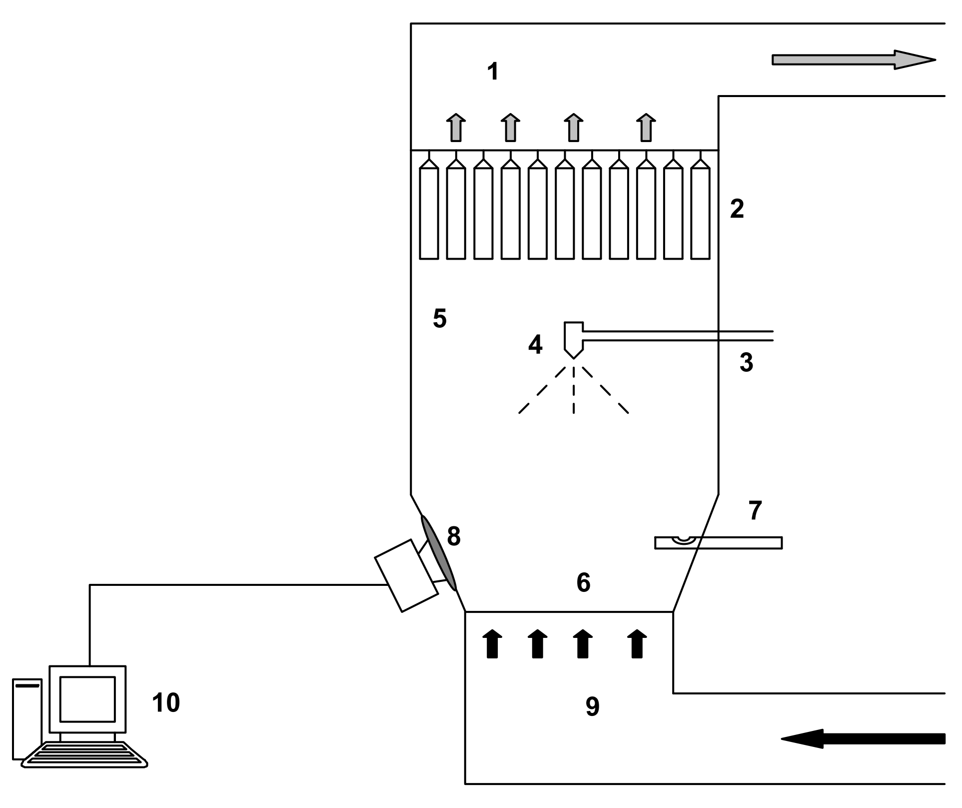

Fig. C-2: *Schematic diagram of fluidized bed granulator WSG 60 with MRT sensor system. 1 = outlet air, 2 = filters, 3 = spray arm, 4 = spray nozzle, 5 = expansion chamber, 6 = product bowl, 7 = sample probe, 8 = MRT sensor system, 9 = heated inlet air, 10 = computer. The mounting position of the sensor system in the granulator GPCG 15 is identical. In contrast to WSG 60 the filters are fixed in the GPCG 15 in two chambers, ensuring a process ran without interruptions.*

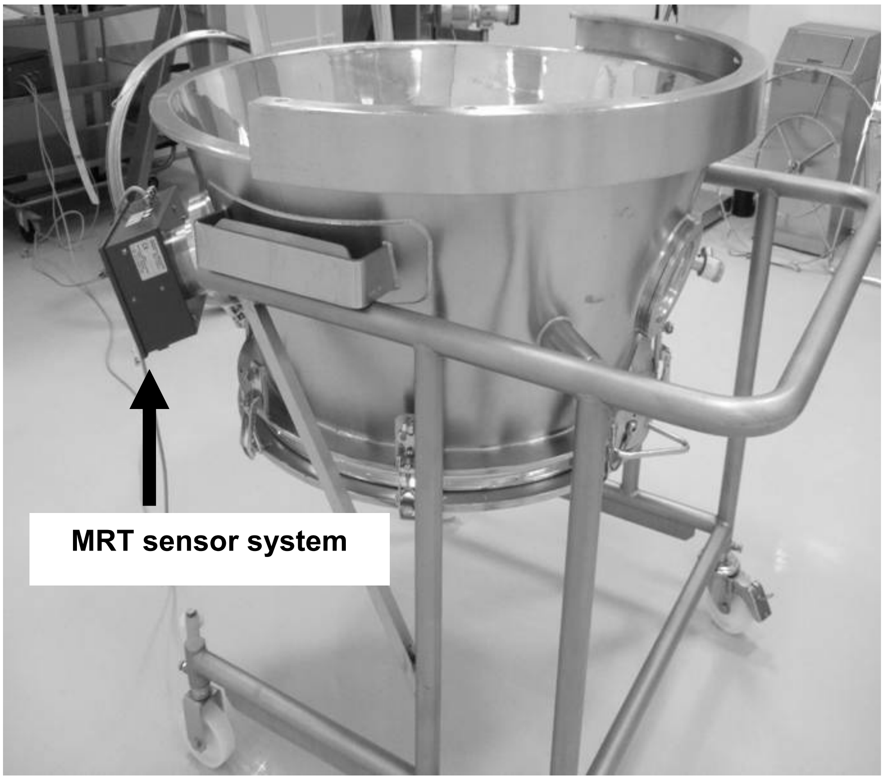

Fig. C-3: *Mounting position of MRT sensor system at the product bowl of the fluidized bed granulator WSG 60*

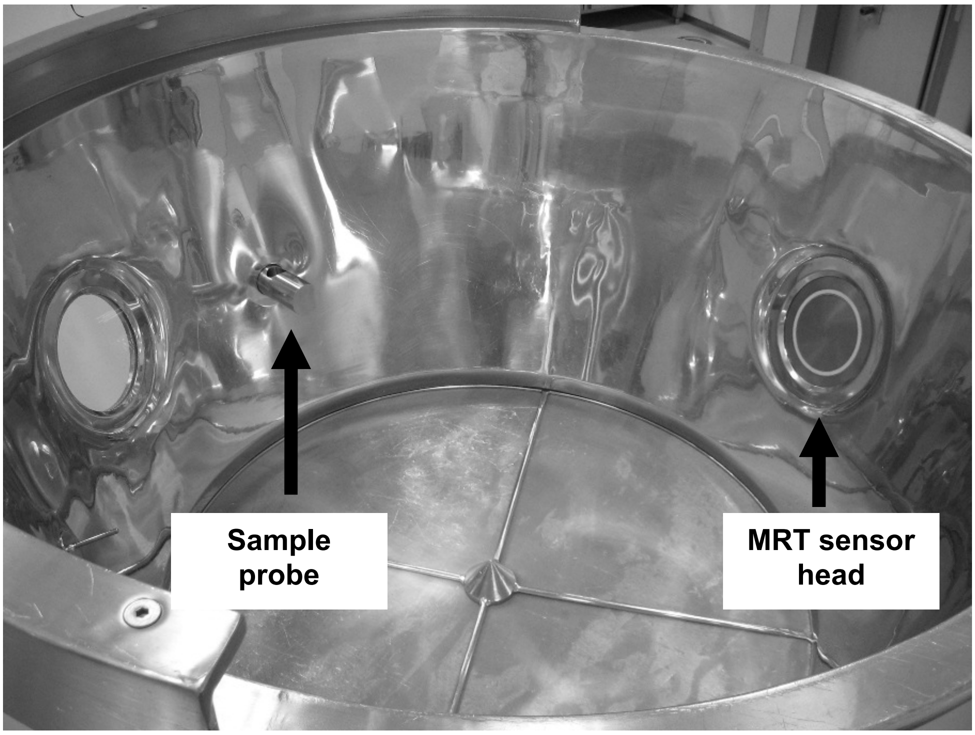

Fig. C-4: *MRT sensor head and sample probe are located at the same height within the product bowl of the fluidized bed granulator WSG 60.*

1.3 Independence of MRT moisture measurement from particle density

In order to use microwave resonance technology for in-line moisture monitoring during fluidized-bed granulation processes, it is essential that the measurement is density independent.

In theory this requirement is met by MRT as the moisture determination is performed by a two parameter measurement. Due to the simultaneous monitoring of frequency shift and bandwidth, the influence of product density is eliminated (see chapter B 5.1). In order to verify this, pre-dried granules were transferred to the fluidized-bed dryer GPCG 15. At predefined time points the inlet air volume was abruptly increased to a higher value for three times. In the initial phase it was adjusted to 500 m³/h and then step by step increased up to 1700 m³/h in the last phase of the process (Figure C-5).

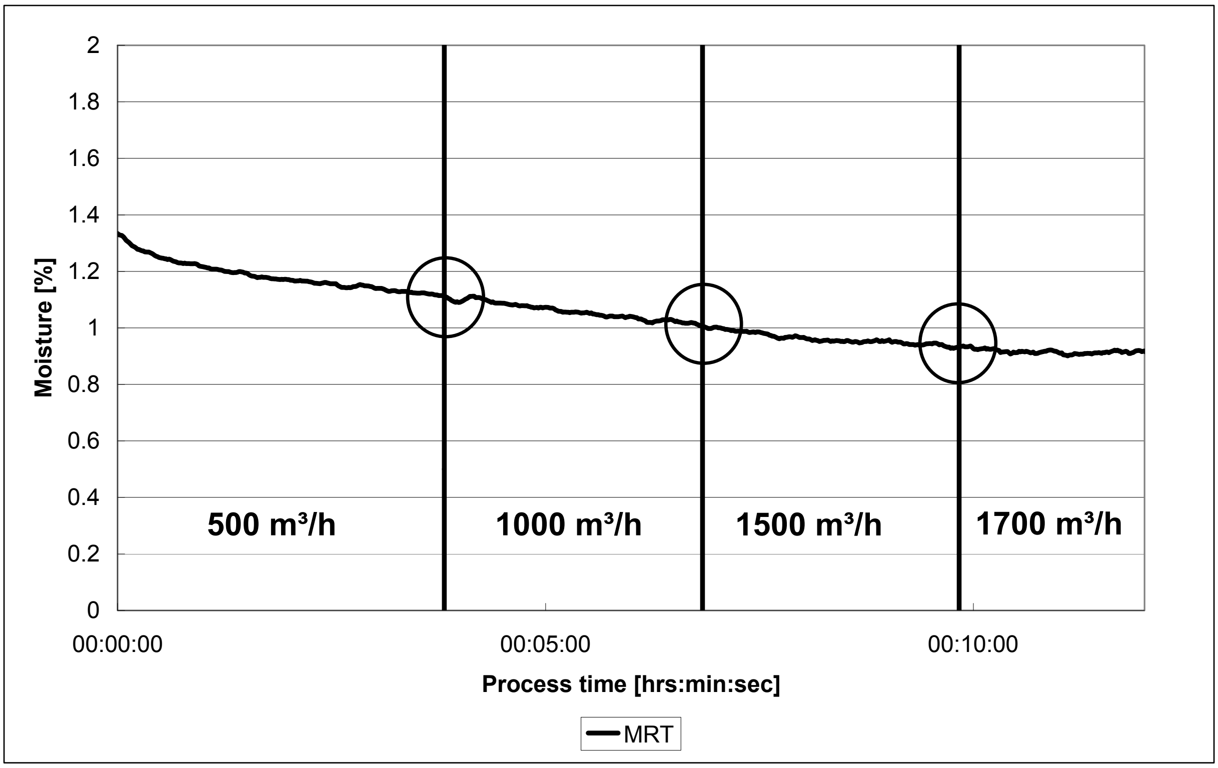

Fig C-5: *Density independence of moisture measurement using the microwave resonance sensor system hydorpharm® fbma (manufacturing device: GPCG 15).*

If the MRT sensor signal is affected by particle density in the sensitive area of the sensor head, the moisture signal is expected to decrease considerably when increasing the inlet air volume. Within these investigations no such phenomenon was recorded.

A minor decrease in the measured moisture content from approximately 1.3 % to 0.9 % was observed. This slight decrease can be traced back to residual drying of the pre-dried granules. Thus, independence of the moisture signal of the MRT signal from the inlet air volume and particle density is verified.

2 Calibration and adjustment of the MRT sensor system

As an indirect method for water determination, microwave resonance technology necessitates the calibration against a direct measuring method e.g. LOD/IR or KF.
In the following, the calibration procedure of the MRT sensor system is given as an example for one crystal-water-free and one crystal-water-containing product. Calibration was performed as described under chapter F 2.2.4.

2.1 Example calibration for one crystal-water-free product

In the following example, adjustment and calibration of the MRT sensor is given for product A consisting of 16 % of one glucocorticoid of group I and 84 % microcrystalline cellulose (MCC). An aqueous solution of 7 % (m/m) povidone 90 was used as a binder. The first five consecutive batches provided training batches and were used for the retrospective adjustment of the MRT sensor system. As reference methods Karl Fischer titration and determination of the loss on drying by infrared light exposure were applied. The results obtained from the off-line methods of the training batches were used for the statistical analysis (F 2.2.4).

Training set MRT versus LOD/IR
For the training set of MRT versus LOD/IR, the granule water content determined by MRT was plotted against the corresponding LOD/IR values (Figure C-6 A). Linear regression revealed the following regression line through the origin (Eq. C-1):

$$y = 1.1623 \cdot x \qquad \text{(Eq. C-1)}$$

y *MRT moisture [%]*
x *LOD/IR moisture [%]*

The correlation coefficient for this regression line was found to be 0.8026. As both reference methods are associated with their own analytical errors, a more reliable coefficient of determination is required. Therefore, Pearson’s correlation coefficient was calculated as it equally considers both methods and is independent of the slope of the regression line. Pearson’s correlation coefficient for the relation of MRT vs. LOD/IR was found to be 0.8775. Covariance for this relation was 0.7893 and residual standard deviation was 0.453. Table C-1 provides a summary of all statistical results.

It is notable that correlating the data from both reference methods, KF and LOD/IR (Figure C-6 C), Pearson's correlation coefficient was 0.9419 and therefore, better than for the correlation of MRT and LOD/IR. Covariance for the relation of both reference methods was determined as 0.8835.

It became obvious that the relation between KF and LOD/IR is much better than the relation between MRT and LOD/IR. But both reference methods are associated with their own analytical errors and feature slightly deviating results due to their measuring principle.

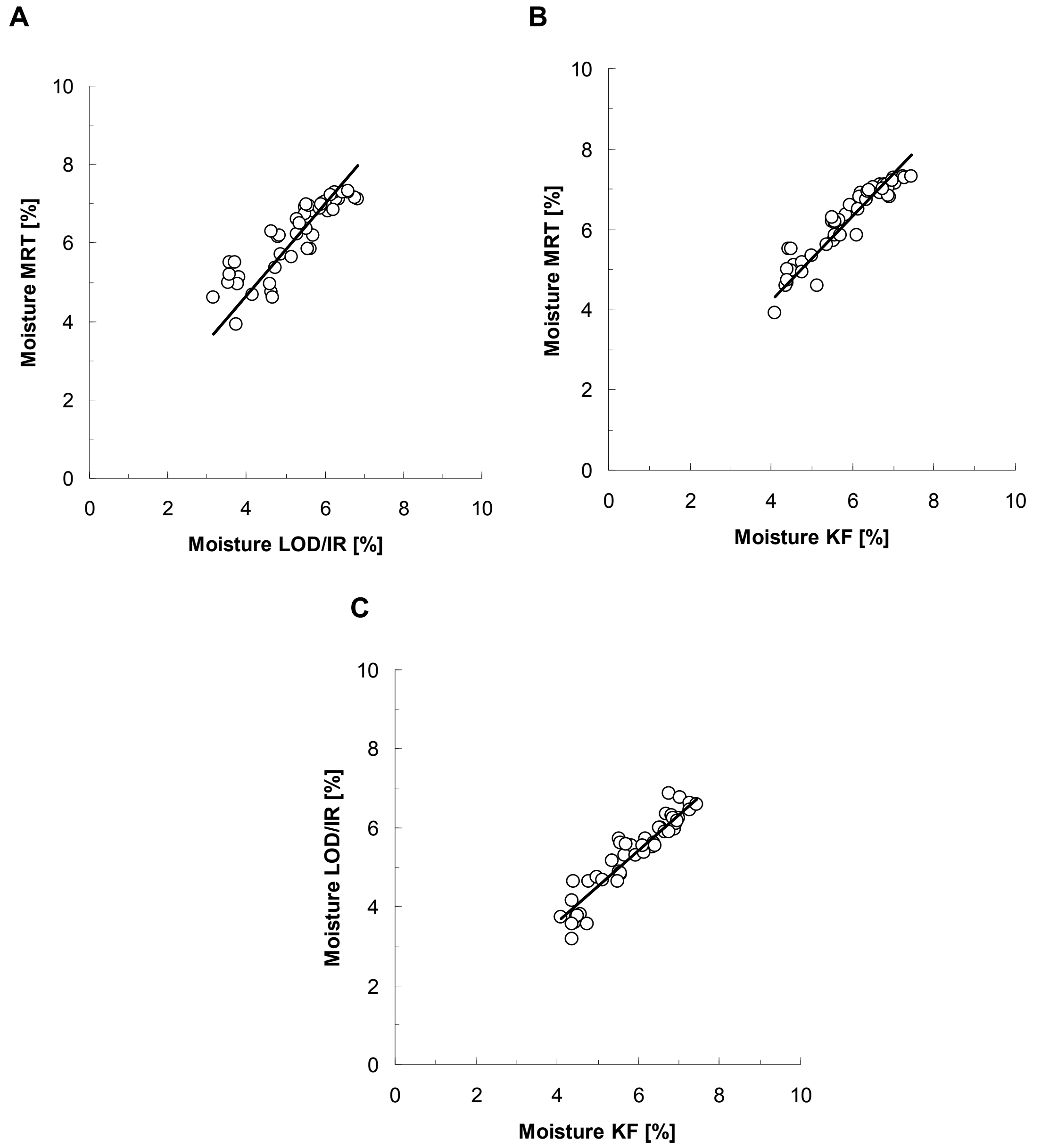

***Fig. C-6**: Linear regressions of moisture measured by MRT, LOD/IR and KF. Data obtained from five training batches.*
***A)** y = 1.1623 x (R = 0.8026), **B)** y = 1.0542 x (R = 0.9341), **C)** y = 0.9030 x (R = 0.9406)*

Test set MRT versus LOD/IR

The equation of the linear regression line of the training batches (Equation C-1) was used to adjust the MRT sensor retrospectively and proceed with six test batches of the same composition. Again a statistical analysis was performed. Thereby Pearson's correlation coefficient improves to 0.9321 (Table C-1). Due to the mathematical correction of the MRT signals, deviations from the ideal line through the origin decrease. Also covariance decreases to 0.3893 and the correlation coefficient (0.9311) and the residual standard deviation (0.243) improved.

Table C-1: *Summary of statistical parameters of the results from the training batches (before correction) and test batches (after LOD/IR respectively KF correction).*
MRT: microwave resonance technology (hydorpharm® fbma sensor), LOD/IR: loss on drying by infrared light exposure, KF: Karl Fischer titration

Statistical parameter	**MRT-LOD/IR**	**MRT – KF**	**LOD/IR - KF**
before correction (training batches)			
Pearson's correlation coefficient	0.8775	0.9468	0.9419
Covariance	0.7893	0.8417	0.8835
correlation coefficient (through 0)	0.8026	0.9341	0.9406
slope regression line	1.1623	1.0542	0.9030
residual standard deviation	0.453	0.304	0.334
after KF correction (test batches)			
Pearson's correlation coefficient	0.9312	0.8040	0.7944
Covariance	0.4200	0.3869	0.3354
correlation coefficient (through 0)	0.9311	0.7821	0.7372
slope regression line	1.0273	1.0083	0.9734
residual standard deviation	0.268	0.424	0.380

Table C-1: *Summary of statistical parameters of the results from the training batches (before correction) and test batches (after LOD/IR respectively KF correction).*
MRT: microwave resonance technology (hydorpharm® fbma sensor), LOD/IR: loss on drying by infrared light exposure, KF: Karl Fischer titration (continuation)

Statistical parameter	MRT-LOD/IR	MRT – KF	LOD/IR - KF
after LOD/IR correction (test batches)			
Pearson's correlation coefficient	0.9321	0.8040	0.7944
Covariance	0.3893	0.3509	0.3354
correlation coefficient (through 0)	0.9311	0.7821	0.7372
slope regression line	0.9318	0.9146	0.9734
residual standard deviation	0.243	0.385	0.380

Training set MRT versus KF

For the training set of MRT versus KF the procedure was identical. The moisture signals recorded in-line by the MRT sensor were plotted against the results of KF water determination, resulting in an approximately linear relationship (Figure C-6 B). The regression line through the origin gives the following equation (Equation C-2):

$$y = 1.0542 \cdot x \tag{Eq. C-2}$$

y *MRT moisture [%]*
x *KF moisture [%]*

In this case the correlation coefficient of 0.9341 was found to be much better than for the regression of MRT and LOD/IR (Table C-1). Pearson's correlation coefficient for MRT-KF of 0.9468 exceeds the coefficient for the correlation of MRT and LOD/IR as well. Furthermore, it is almost the same as the correlation coefficient of both reference methods. Also the residual standard deviation, calculated for MRT-KF (0.304) is better than for MRT-LOD/IR (0.453). Comparing the relation between MRT-LOD/IR and MRT-KF of the training set it becomes obvious that KF data corresponds better with MRT signals than LOD/IR.

Test set MRT versus KF

As described previously the regression line of MRT-KF training (Equation C-2) was used to adjust the MRT sensor retrospectively, by applying a correction factor of 1.0542 for subsequent test batches. Thus, the slope of the resulting regression line (1.0083) approached the ideal value of 1.000, indicating an almost perfect linear relationship.

However, the Pearson’s correlation coefficient did not improve in the test set (0.8040) compared to the training set (0.9468). The residual standard deviation changed slightly for the worse (0.424). The calculation of the residues to the fitted line reveals that the data points scatter randomly around zero, independent of the moisture determined by KF (Figure C-7 B). In comparison Figure C-7 A shows that the calculated residues of the uncorrected MRT signals feature a strong tendency to negative values. For the relationship between MRT and LOD/IR, the calculated residues also showed a considerable tendency to negative values before correction, (Figure C-7 C) and to positive values after correction (Figure C-7 D).

Furthermore, it became obvious that the correlation of the test batches for both MRT-LOD/IR and MRT-KF is stronger than the relation between both reference methods against themselves (Table C-1).

Due to the results of the statistical analysis and the fact that the residues calculated after LOD/IR correction showed a tendency to positive values it was decided to perform calibration against KF for the in-line measurement of further granule batches with this composition.

However, it is important to know that the standard calibration of the sensor as initially delivered by the supplier is quite good for the investigated granulation process.

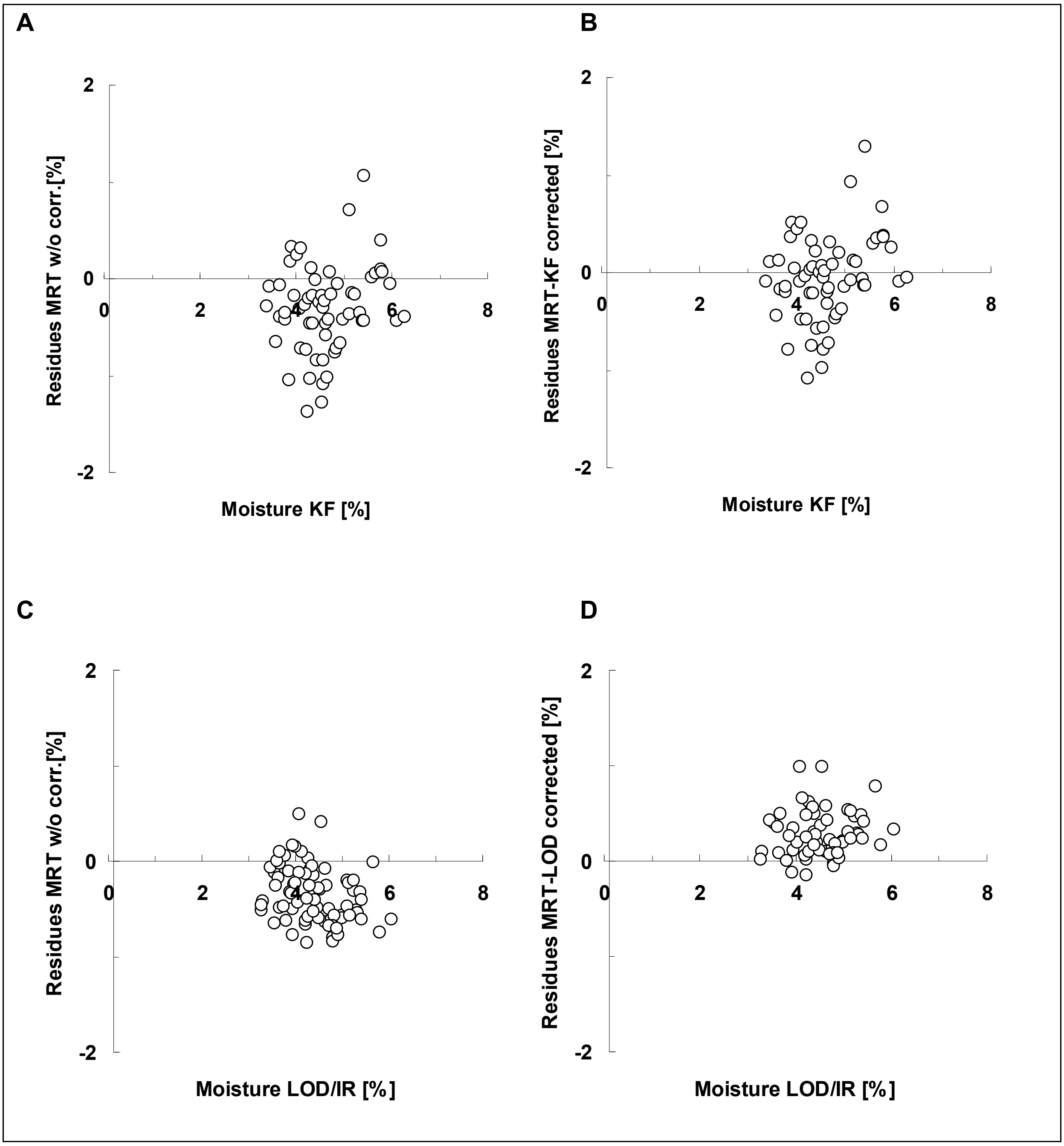

Fig. C-7*: Residues of microwave resonance technology (MRT) moisture [%] of the test batches.*

A) *MRT moisture [%] plotted against KF [%] without correction.*

B) *MRT moisture [%] plotted against KF [%] with data correction on KF results from training set results.*

C) *MRT moisture [%] plotted against LOD/IR [%] without correction.*

D) *MRT moisture [%] plotted against LOD/IR [%] with data correction on LOD/IR results from training set results.*

2.2 Example calibration for one crystal-water-containing product

Within this study the granulation processes of many products containing crystal-water were measured in-line by MRT. Due to the proportion of crystal-water, which can only be determined under particular conditions, calibration was quite challenging. While KF determines all water types including crystal-water, neither LOD/IR nor MRT can detect this water type. However, for the determination of the drying endpoint, only the fraction of free water is important. Chrystallographically bound water can be neglected.

The following gives an example of the calibration procedure of a crystal-water-containing product.

Product B consisted of 68 % α-Lactose monohydrate and 32 % maize starch (process conditions are listed in chapter F 2.1.1). The fraction of crystal-water was calculated to be approximately 3.4 %. For calibration and adjustment the first two batches were used as training batches and the third provided as a test batch.

Training set MRT versus LOD/IR

The moisture signals recorded in-line by the MRT sensor system were plotted against the results of the off-line water determination by LOD/IR. The resulting graph is displayed in Figure C-8.

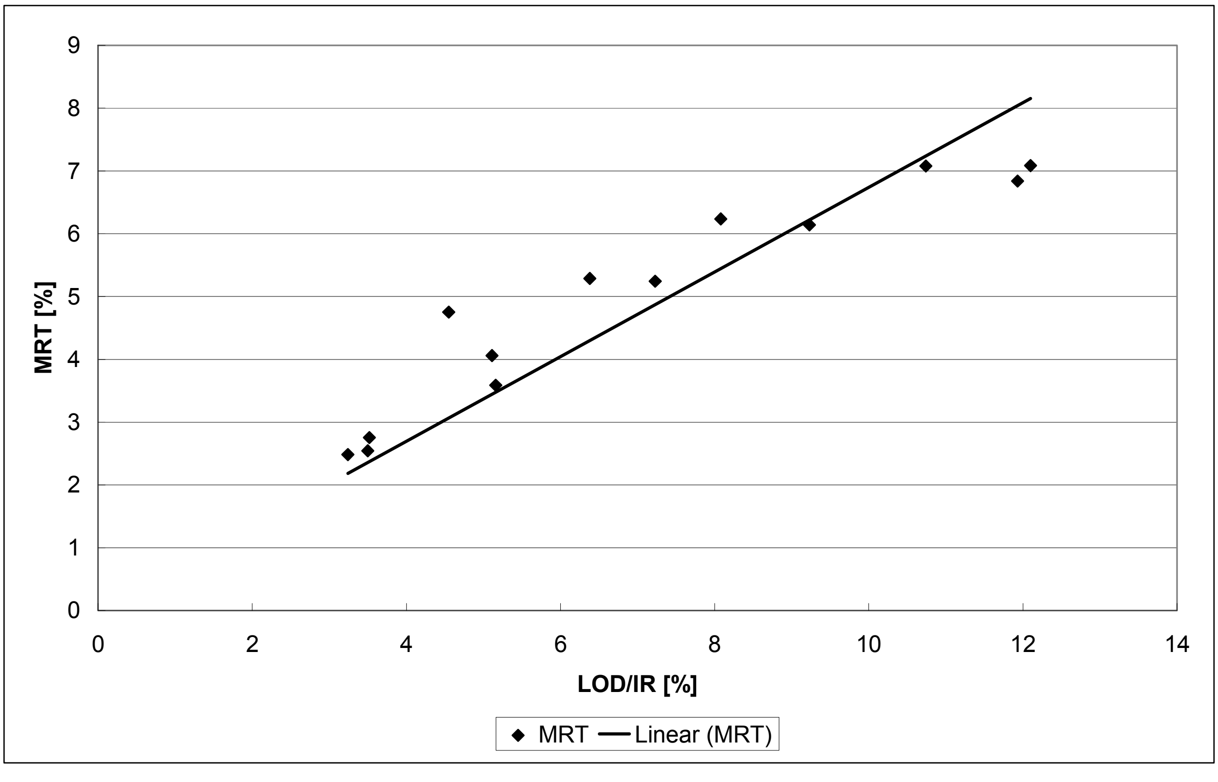

Fig. C-8: *Correlation of the moisture [%] recorded in-line by MRT and the reference method LOD/IR. y = 0.6739x, (R = 0.8817)*

Evaluating the above graph an interesting phenomenon was found. At moisture contents > 8.5 % increasing residuals between the MRT moisture values and the reference method were found. For the relationship of MRT and KF the same effects were observed (see Figure C-10). At that time, no explanation for the deviating results at higher moisture contents was available. Therefore, subsequent studies have focused on that aspect (see chapter C 8). For the endpoint determination of the drying process of this product, a reliable moisture determination at the range of water contents < 5 % was required. Thus, the increasing deviations at moisture contents > 8.5 % were neglected and calibration for this product was performed for moisture measurements up to 8.5 %.

Figure C-9 displays the resulting graph for the relation of MRT – LOD/IR < 8.5 %.

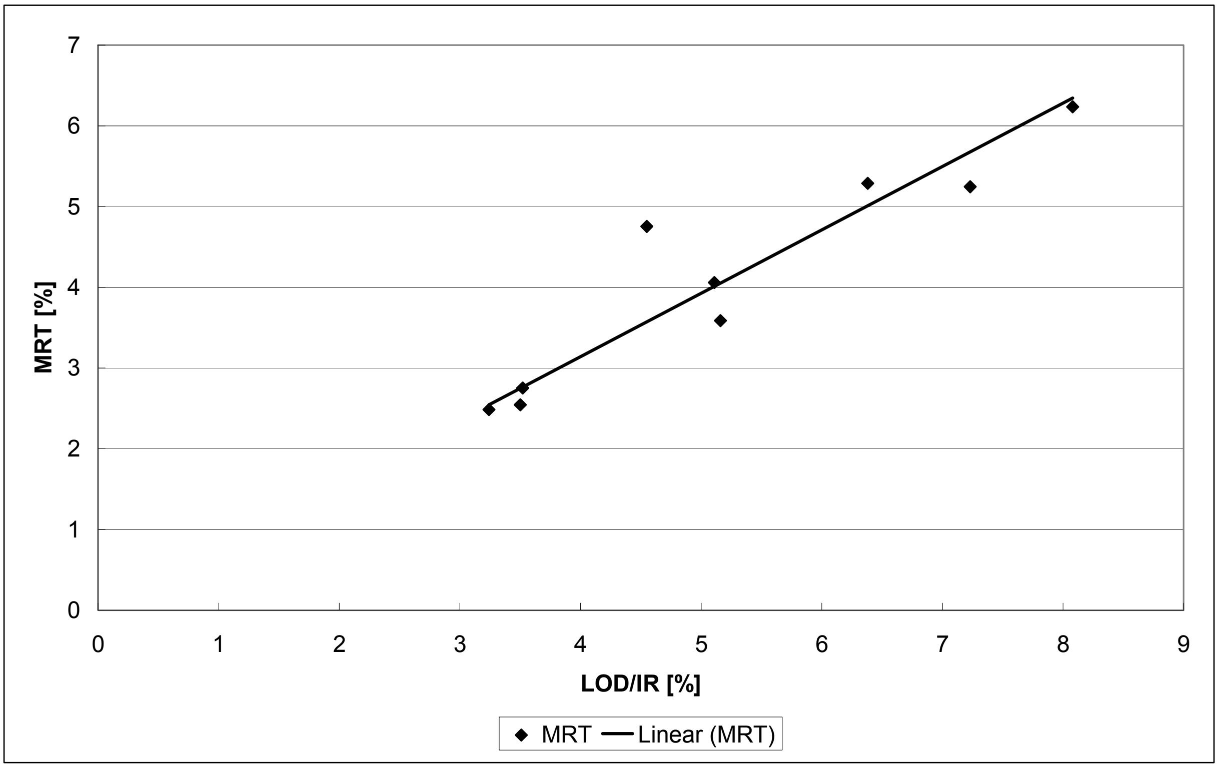

Fig. C-9: *Correlation of moisture [%] < 8.5 % recorded in-line by MRT and the reference method LOD/IR. y = 0.7853x, (R = 0.9325)*

The regression line through the origin features following equation (Equation C-3):

$$y = 0.7853 \cdot x \qquad \text{(Eq. C-3)}$$

y *MRT moisture [%]*
x *LOD/IR moisture [%]*

For the relation of MRT against LOD/IR, Pearson's correlation coefficient was found to be 0.9346. (Table C-2). The correlation coefficient was 0.9325 and the residual standard deviation was found to be 0.517.

Test batch MRT versus LOD/IR

The equation of the linear regression line of the training batches (Equation C-3) was used to adjust the MRT sensor retrospectively and proceed with one test batch of the same composition.

Due to the adjustment of the sensor signal Pearson's correlation coefficient improved to 0.9973. The deviations from the ideal line through the origin decreased considerably. The correlation coefficient through the origin improved as well (see Table C-2). Also the residual standard deviation (0.158) improved remarkable after LOD/IR correction.

Table C-2: *Summary of statistical parameters of the results from the training batches (before correction) and test batches (after LOD/IR respectively KF w/o cw correction). For calibration moisture values < 8.5 % were considered.*

Statistical parameter	MRT-LOD/IR	MRT – KF w/o cw	LOD/IR – KF w/o cw
before correction (training batches)			
Pearson's correlation coefficient	0.9346	0.9190	0.9900
correlation coefficient (through 0)	0.9325	0.9190	0.9868
slope regression line	0.7853	0.7673	0.9771
residual standard deviation	0.517	0.574	0.260
after KF w/o cw correction (test batch)			
Pearson's correlation coefficient	0.9973	0.9900	0.9938
correlation coefficient (through 0)	0.9926	0.9898	0.9877
slope regression line	1.0037	0.9251	0.9205
residual standard deviation	0.162	0.309	0.256
after LOD/IR correction (test batch)			
Pearson's correlation coefficient	0.9973	0.9900	0.9938
correlation coefficient (through 0)	0.9926	0.9900	0.9877
slope regression line	0.9807	0.9039	0.9205
residual standard deviation	0.158	0.302	0.256

Training set MRT versus KF

In order to compare KF results with MRT and LOD/IR, the fraction of crystal water, in this case 3.4 % had to be subtracted from the original KF results. To evaluate the correlation between MRT and KF, the results of the in-line water determination were plotted against the corrected KF results (Figure C-10).

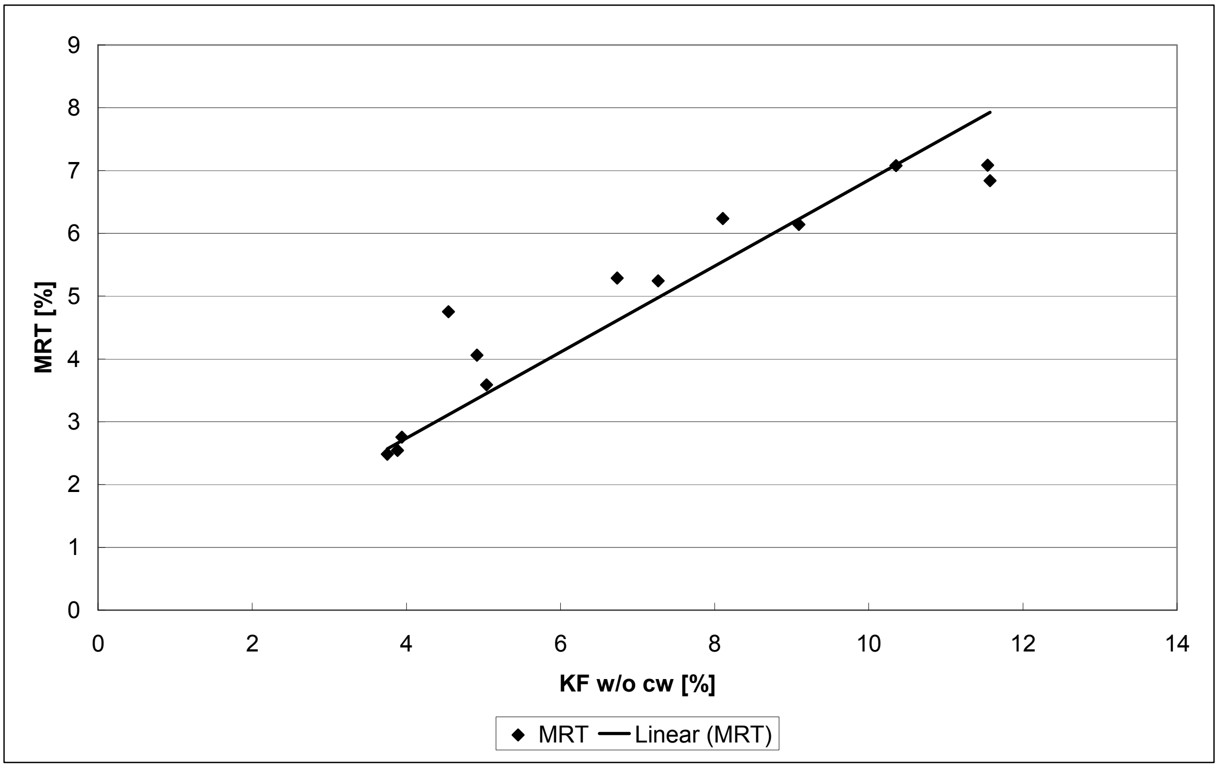

Fig. C-10: *Correlation of the moisture [%] recorded in-line by MRT and the reference method KF (without crystal water). y = 0.6849x, (R = 0.9101)*

The previous observations of increasing deviations between MRT-LOD/IR were verified for MRT-KF. As mentioned, moisture values up to 8.5 % were considered for calibration. Figure C-11 displays the MRT values plotted against the respective KF results < 8.5 %.

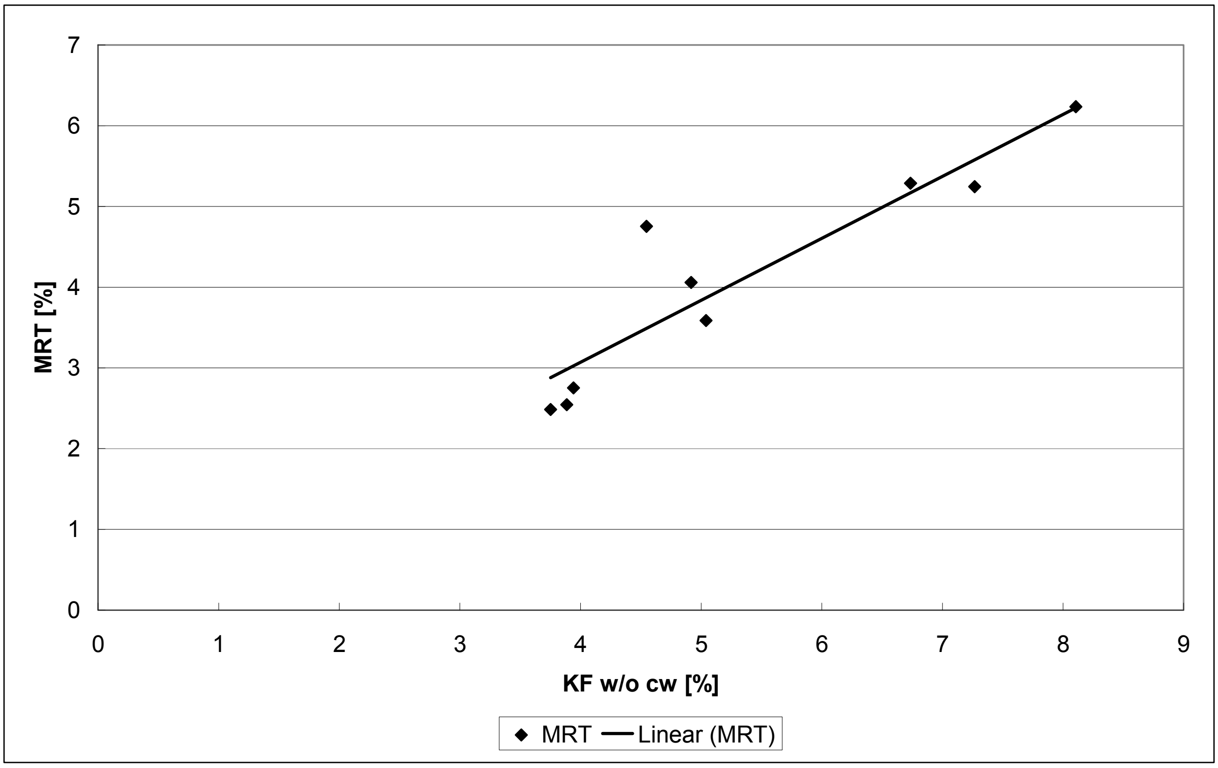

Fig. C-11: *Correlation of moisture [%] < 8.5 % recorded in-line by MRT and the reference method KF w/o cw. y= 0.7673x, (R= 0.9190)*

The following equation for the linear regression line through the origin results:

$$y = 0.7673 \cdot x \qquad \text{(Eq. C-4)}$$

y *MRT moisture [%]*
x *KF moisture [%]*

Both the correlation coefficient and Pearson's correlation coefficient were calculated to be 0.9190 (see Table C-2). In comparison to the relationship between MRT and LOD/IR, both values were found to be lower for MRT and KF. This may be caused by the fact that KF results had to be corrected mathematically due to the fraction of crystal-water prior to the statistical analysis. The residual standard deviation was quite similar for MRT-KF (0.574) and MRT-LOD/IR (0.517).

Test set MRT versus KF

The resulting equation C-4 was used for the retrospective adjustment of the sensor system for one test batch. The mathematical correction of the MRT sensor signal led to an improvement of both the correlation coefficient (0.9898) and Pearson's correlation coefficient (0.9900). Furthermore, the residual standard deviation improved to 0.309.

The differences of the relationship between both reference methods after the adjustment of the MRT sensor versus LOD/IR and KF were found to be marginal. In both cases the relationship between the corrected MRT values and the corresponding off-line results of the reference methods improved in comparison to the uncorrected relationship. Also the slopes of the regression lines are slightly better for both relationships after the sensor adjustment on KF (see Table C-2).

2.3 Conclusion

Calibration of the MRT sensor system was performed successfully for crystal-water-free and crystal-water-containing products. In both cases calibration against KF as direct method for water determination was proved to be suitable if the proportion of crystal water contained in the product is subtracted from the original KF results. However, the standard calibration of the sensor system was found to be suitable for a reliable moisture determination of both products.

3 Monitoring of the drying process of crystal-water-free granules

The identification of the drying endpoint of fluidized bed processes is of crucial importance to guarantee product quality. Up till now, the determination of the drying endpoint of fluidized bed processes was challenging. Either indirect parameters, such as the exhaust air temperature, or off-line methods like LOD/IR were used. Therefore, it was of major interest to establish a technique that allows the direct determination of the process endpoint in real time. This issue was the main focus at the beginning of this study.

3.1 Moisture monitoring

In a first measuring run drying processes of product A were monitored by MRT. The powder blends consisted of 16 % of a crystal-water-free glucocorticoid (group I) and 84 % MCC. Both excipients were mixed in the fluidized bed granulator WSG 60 under GMP conditions. The granulator was equipped with the MRT sensor system enabling in-line monitoring of granule moisture throughout the drying process. The batch size was 53 kg. Calibration and adjustment of the sensor system for this product was performed in accordance to KF results (see chapter C 2.1). A summary of the process conditions is given in chapter F 2.1.1.

Wet granulation was started by spraying 17.4 kg of an aqueous solution of 7 % (m/m) povidone 90, after a product temperature of approximately 38 °C was reached. As soon as the binder was completely added, drying of the wet granules started.

According to the product specification, a residual granule water content of ≤ 3.8 % was required. The drying process of the first granule batch was monitored discontinuously as per former practice. At predefined time points, samples were withdrawn and analyzed off-line by LOD/IR. While the water content was determined the drying process was interrupted and fluidisation stopped. Afterwards, it was possible to decide whether the drying process could be stopped, as the endpoint has been reached, or if granules had to be further dried or moistened. Additionally, the MRT signals were recorded in-line and compared to the off-line results (Figure C-12).

Drying of this granule batch started with a residual water content of approximately 5.5 %. The process had to be stopped six times for sample withdrawal and off-line water determination until the specified residual water content of < 3.8 % was reached. Due to the missing fluidisation the MRT sensor recorded nearly constant moisture values during the process interruptions for off-line analysis (Figure C-12).

After a drying time of approximately one hour, the specified endpoint was reached and the process was stopped. A good correlation between the moisture measured in-line by MRT and the reference method LOD/IR was observed throughout the entire drying process.

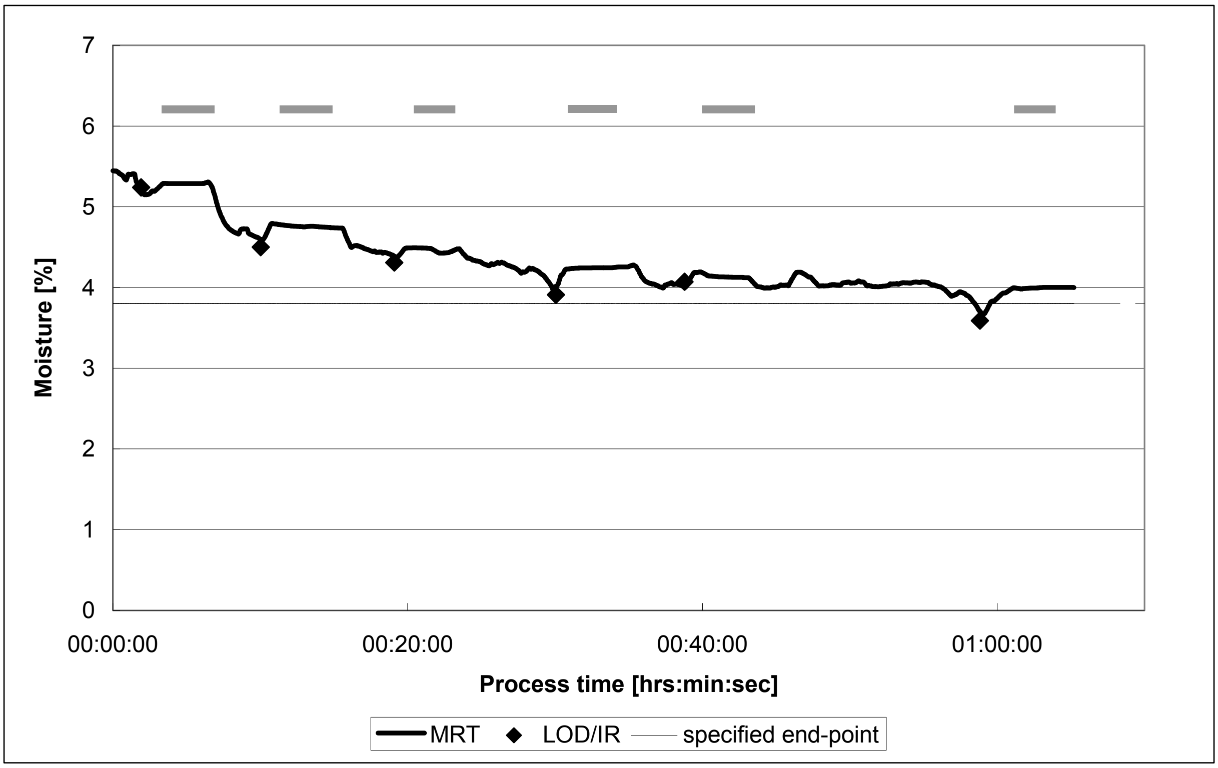

Fig. C-12: *Drying process of a crystal-water-free granule batch recorded in-line by the MRT sensor system and off-line by the reference method LOD/IR (manufacturing device: WSG 60). Process control was performed discontinuously by LOD/IR.* ▬ *Process interruptions for sampling and off-line analysis.*

Afterwards, a second granule batch with the same composition was produced under comparable conditions. However, the drying process was not interrupted for sample withdrawal and time consuming off-line water determination. Instead, in-line monitoring of granule moisture using the MRT sensor was directly used for process control and measurement. Thus, the process ran continuously until the specified residual granule water content was reached and then a sample was withdrawn for off-line moisture measurement. The drying process of the second granule batch started at a moisture of approximately 5.9 % (Figure C-13).

Due to the continuous drying of the wet granules, the specified endpoint was reached after a drying time of approximately 12 minutes. As the product specification demands the determination of moisture content by LOD/IR, samples were withdrawn and analyzed off-line. For batch 1 and 2, the results were in very good agreement with the moisture measured in-line by MRT (Figure C-13).

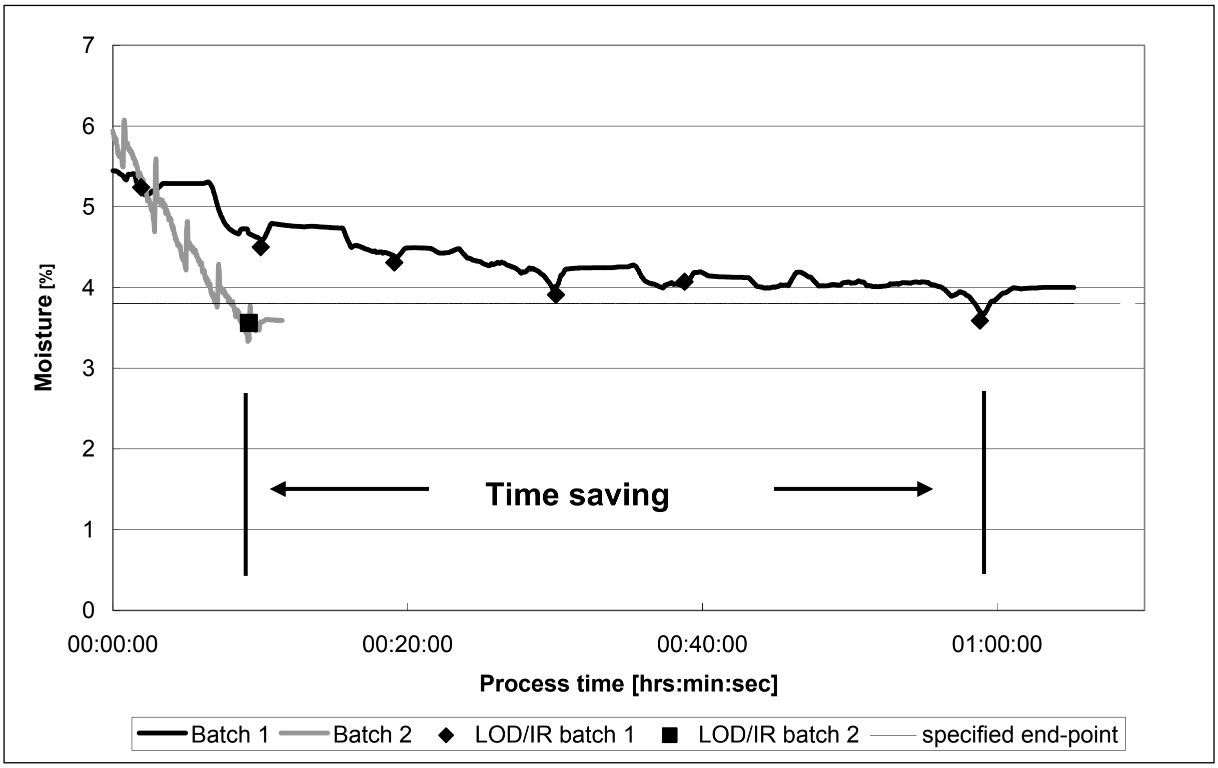

Fig.C-13: *Time saving during the drying process due to a continuously monitored process (batch 2) by MRT instead of discontinuous process control (batch 1) by LOD/IR (manufacturing device: WSG 60).*

Comparing the off-line (first batch) and in-line (second batch) monitoring of the granule moisture a time-saving of about 45 minutes was achieved. This is equivalent to 75 % of the total drying process time.

It is obvious that the risk of critical changes to the physicochemical properties of the granules can be significantly minimized performing in-line monitoring of granule moisture by MRT. Discontinuous moisture determination may cause an inhomogeneous drying of the solid material. During off-line determination, the fluidisation was stopped and the granules rest at the bottom of the product container. During this time, the granules located in the middle of the product container could get wet again. In contrast, the granules located at the heated walls could further dry. Therefore, it is questionable whether it is possible to ensure that, after the analysis time the results obtained by off-line water determination are still valid compared to the actual water content of the granules in the fluidized bed granulator. Furthermore, off-line monitoring of granule moisture delivers the results of the samples after some time-delay. It is difficult to gain a deeper insight into the actual moisture state.

In addition to the moisture course one further interesting phenomenon was observed. Throughout the entire drying process, maxima in the granule moisture track were found at regular intervals. Temporally, they correlate exactly with periodically induced vibrations of the fine particle filters of the granulator, as a part of the cleaning process. Similar observations were reported by Schmidt-Lehr (2007) within their investigations on the on-line monitoring of particle sizes using a laser probe in fluidized bed granulation. Obviously, the vibration of the fine particle filters influence not only the moisture measurement, but also the entire drying process. This is most probably caused by continuously detaching fines from the fluidized bed to the filters and then discharging them to the bed periodically.

3.2 Conclusion

Microwave resonance technology was successfully established for the endpoint determination of fluidized bed drying processes of crystal-water-free granules. In-line moisture monitoring using the MRT sensor system has been proven to be precise and accurate. A good correlation to the reference method LOD/IR was achieved. Furthermore, a considerable time-saving of the drying process was achieved using MRT for process control. Continuous in-line moisture measurement is associated with a reduction of different risks, caused by process interruptions for sample withdrawal and off-line moisture determination. Hence, product quality is ensured. The MRT sensor system turns out to be a valuable tool for conforming to FDA’s PAT approach.

4 Monitoring of the drying process of crystal-water-containing granules

In order to verify the use of the MRT sensor system for the endpoint determination of crystal-water-containing granules, the drying processes of two different products were monitored in-line by MRT.

4.1 Moisture monitoring

In a first measuring run, the drying process of product B was monitored in-line. Wet granules consisting of 68 % α-Lactose monohydrate and 32 % Maize starch were produced in a V-blender using purified water as a granulating fluid. Afterwards, the wet granules were manually transferred into the fluidized bed granulator WSG 60 for drying. Throughout the drying process, samples were withdrawn at predefined time points in order to determine their water content off-line by KF and LOD/IR. As described under chapter C 2.2, sensor adjustment was performed in accordance to KF.

Figure C-14 displays the moisture track of an example batch of product B and the results of the reference methods.

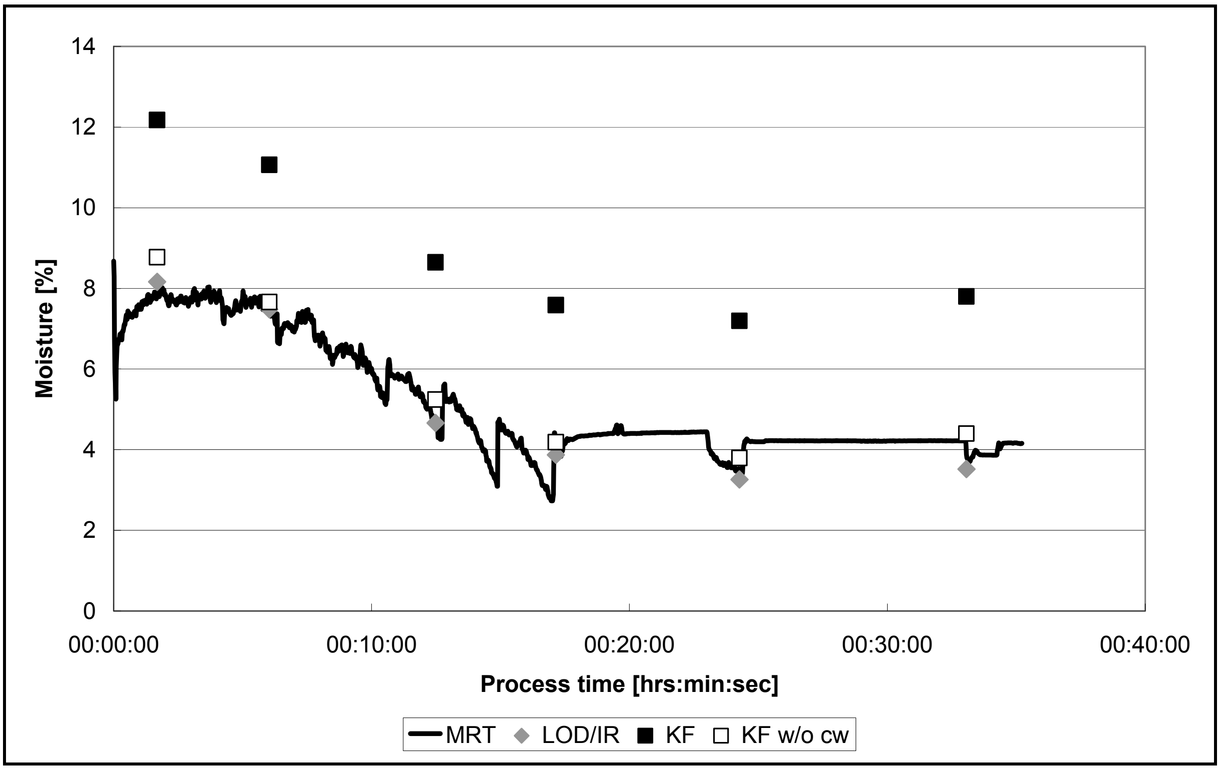

Fig. C-14: *Moisture [%] track of product B throughout the drying process recorded in-line by the MRT sensor system and off-line by LOD/IR, KF and KF without crystal water (KF w/o cw). (manufacturing device: WSG 60).*

Due to the fraction of crystal-water, the original KF values exceed both the MRT and LOD/IR values considerably. After the subtraction of the crystal-water percentage (3.4 %) a good correlation of all three methods was observed. A reliable endpoint determination was possible.

To verify this result, the drying process of one further crystal-water-containing product was monitored in-line. Powder blends of product C consisting of 33 % MCC and 67 % α-Lactose monohydrate were mixed in a high-shear mixer under experimental conditions. Wet granulation was performed applying 1.7 kg aqueous solution of 10 % (m/m) povidone 90. The batch size was 6 kg. After passing the wet granules through a 5 mm wet sieve, the granules were manually transferred to the fluidized bed apparatus GPCG 15. The granulator was equipped with the MRT sensor system and a standard 100 µm PZ bottom sieve plate. The drying process was monitored continuously using the MRT sensor, as well as discontinuously by LOD/IR.

For the off-line water determination, samples were withdrawn throughout the entire process and compared to the moisture values measured in-line by microwave resonance technology. Furthermore, the results obtained were used to calibrate the sensor by calculating granule-specific correction factors using the delivered software.

Figure C-15 displays the moisture track of the granule batch throughout the entire drying process recorded by the MRT sensor and the moisture values determined off-line by the reference method LOD/IR.

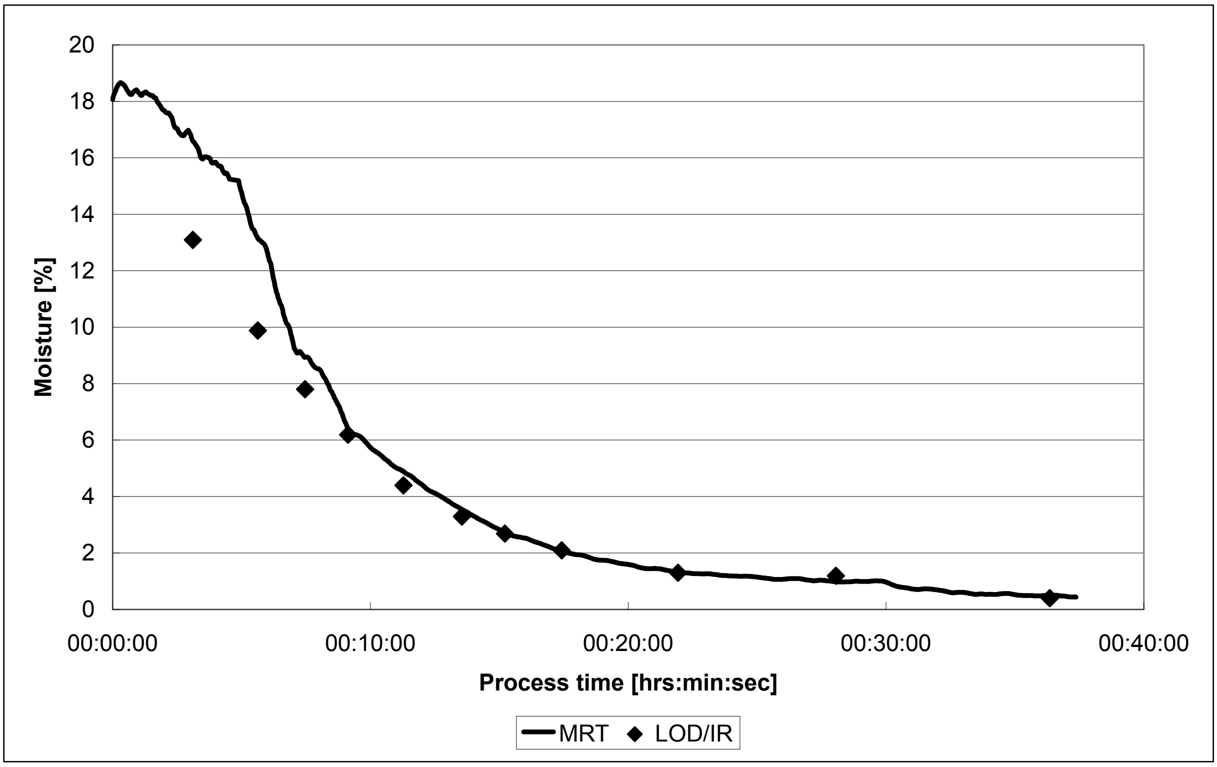

Fig. C-15: *Moisture [%] track of product C throughout the drying process recorded in-line by MRT and off-line by LOD/IR (manufacturing device: GPCG 15).*

Drying of the wet granules was started with a residual water content of approximately 18 %. After a drying time of approximately 37 minutes the moisture content of the granules was 0.4 %. By comparing the in-line data with the results determined off-line, a strong correlation of both methods at moisture contents < 8 % was achieved. However, remarkable deviations were registered for moisture contents above 8 %. This effect was investigated within following experiments (see chapter C 8). Only small discrepancies between MRT and LOD/IR results were found for moisture contents < 3 %.

Various batches of product C were produced under comparable process conditions (see F.2.1.1) in order to verify repeatability of the moisture measurement by MRT. Figure C-16 illustrates the moisture courses of all batches monitored in-line by the MRT sensor and their respective moisture values determined off-line by LOD/IR.

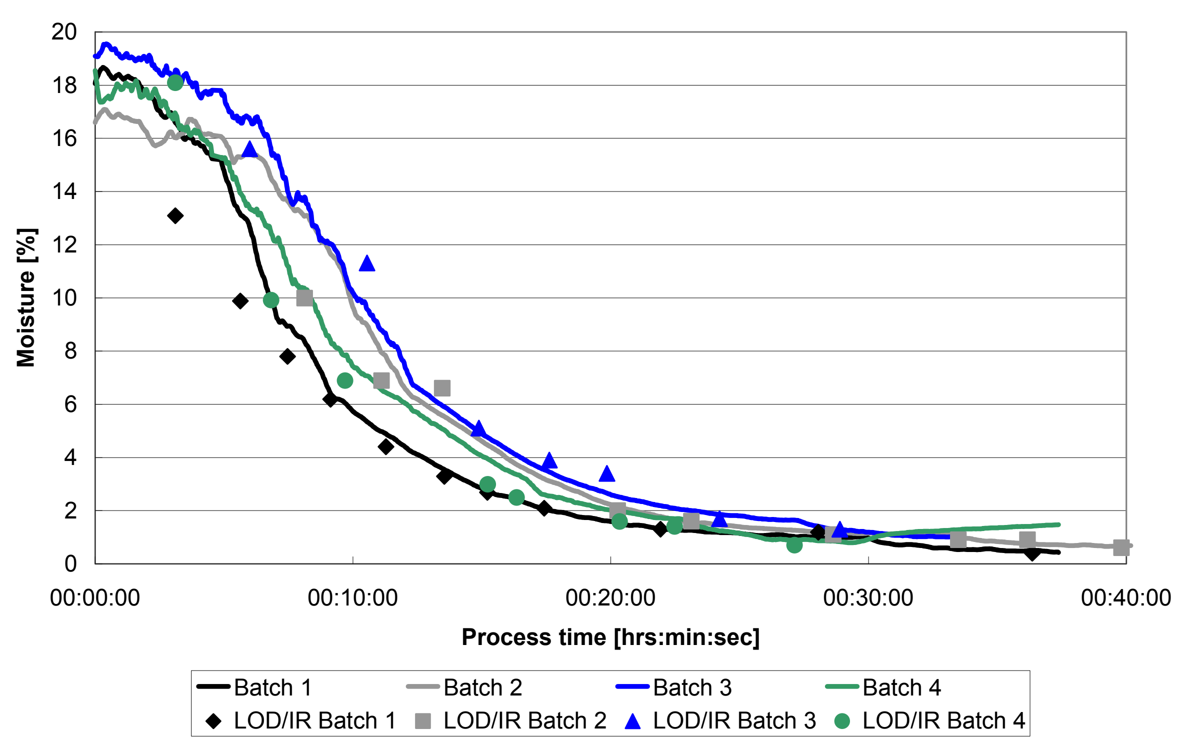

Fig. C-16: *Repeatability of moisture monitoring [%] of product C by MRT during fluidized bed drying processes (manufacturing device: GPCG 15).*

In all batches, the water content of the granules correlated well with the results obtained by LOD/IR for moisture contents < 8 %. Above this moisture value remarkable deviations were recorded for all batches.

It is obvious that moisture courses of the batches also showed good agreement with each other. Nevertheless, slight deviations of the moisture at the beginning of the drying process and in the following moisture courses were observed. Several reasons are possible. On the one hand, the granulator GPCG 15 operated with unconditioned inlet-air. Therefore, slight influences on the moisture course due to a dependency on environmental moisture are possible. On the other hand, it is possible that the raw materials themselves varied slightly in their initial water content.

Figure C-17 displays the moisture values recorded by the MRT sensor plotted against the results of external water determination by LOD/IR. The resulting regression line showed a good correlation coefficient of 0.976. Increasing deviations between the results of both methods at water contents > 10 % became observable. However, in the region of low water content, which is crucial for endpoint monitoring, a very good correlation between both methods was achieved.

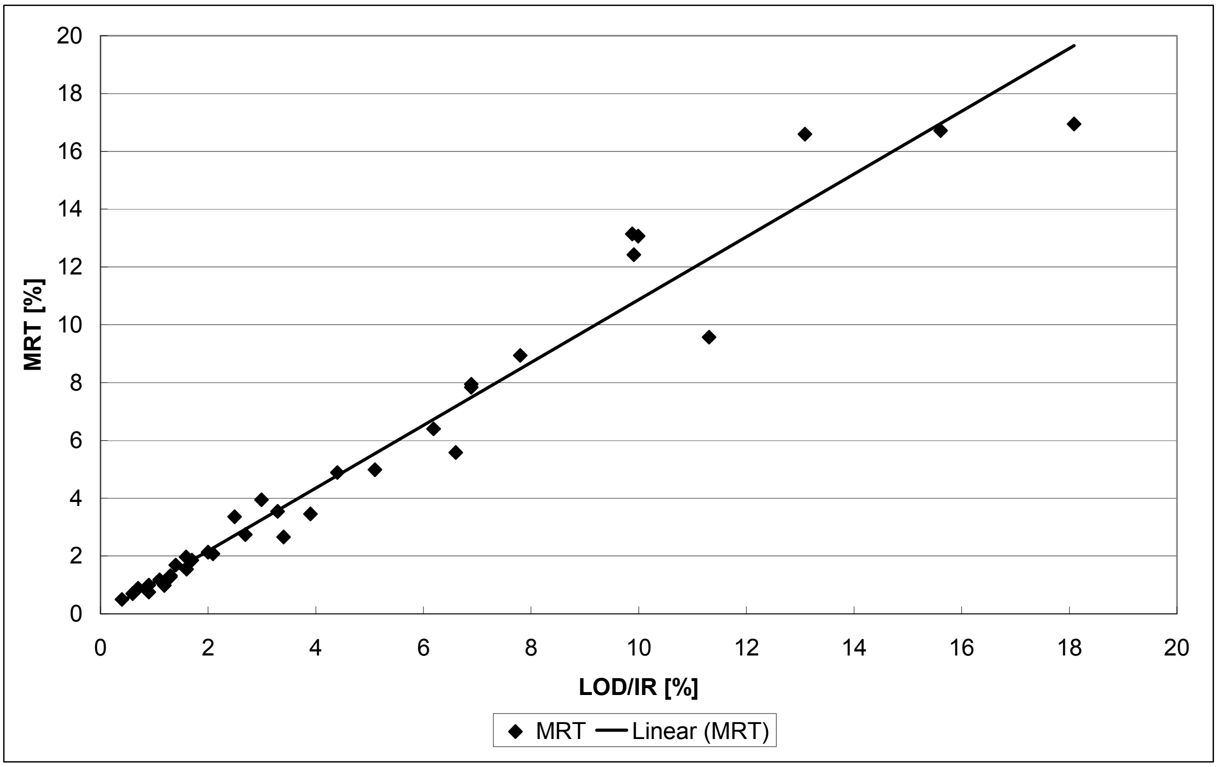

Fig. C-17: *Correlation of moisture [%] recorded in-line by MRT and off-line by LOD/IR of product C. y = 1.0864x, (R = 0.976)*

The calculation of the residues demonstrates that the deviations between MRT and LOD/IR results increased with rising moisture contents (see Figure C-18).

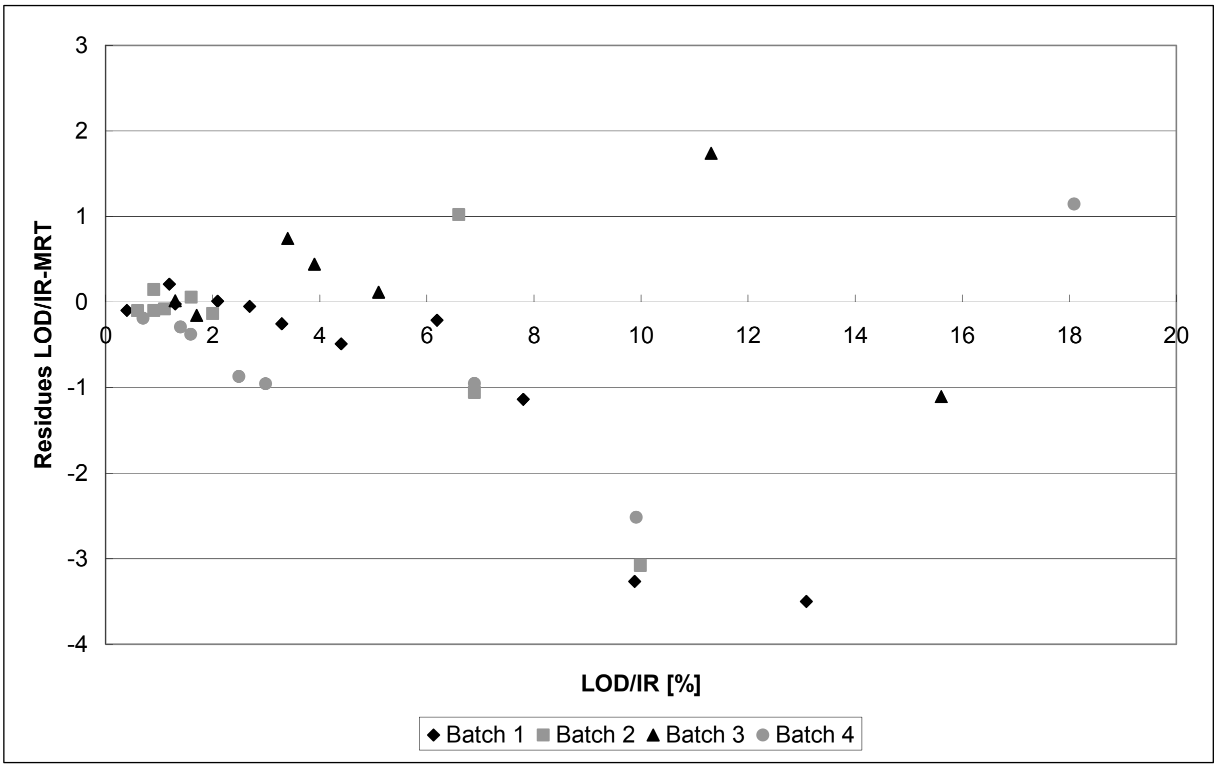

Fig. C-18: *Residues of MRT moisture [%] plotted against the water contents determined by LOD/IR.*

In the range of water contents < 5 %, the data points scatter randomly around zero and residues were found to be very low. Above a granule water content of 10 %, residues have increased noticeably with a slight tendency to negative values.

Within the following experiments, the phenomenon of increasing deviations between the in-line and off-line methods at higher water contents were investigated in more detail (see chapter C 8).

4.2 Conclusion

The microwave resonance sensor system was proven to be a valuable tool for the identification of the drying endpoint of crystal-water-containing granules. A good correlation with the results of the off-line reference method LOD/IR was obtained. Contrary to MRT and LOD/IR, KF detects crystal-water as well. To compare the recorded MRT moisture with the results of the water determination by KF, the fraction of crystal water, contained in the product, had to be first subtracted from the original KF results. Afterwards both methods correlated well.

At higher moisture contents increasing deviations between MRT and both reference methods were observed. The thorough investigation of this phenomenon was performed within subsequent studies (see chapter C 8).
A reliable and reproducible moisture monitoring and identification of the drying endpoint was achieved for both crystal-water-containing products.

5 Monitoring of the entire wet granulation process of crystal-water-free granules

Up till now the focus of the investigations was on the identification of the drying endpoint of wet granulation processes. As it is reported that the moisture significantly influences final product quality [Serno 2007], the MRT sensor system was used for the moisture monitoring of the entire wet granulation process. In addition to the determination of the drying endpoint, the aim of this investigation was to gain further information about the process flow and to improve process understanding.

5.1 Moisture monitoring

Various batches of product A consisting of 16 % water-free-crystals of a glucocorticoid of group I and 84 % MCC were produced. An aqueous solution of 7 % (m/m) of povidone 90 was applied as a binder. The granulation processes were performed in the fluidized bed granulator WSG 60 under GMP conditions.

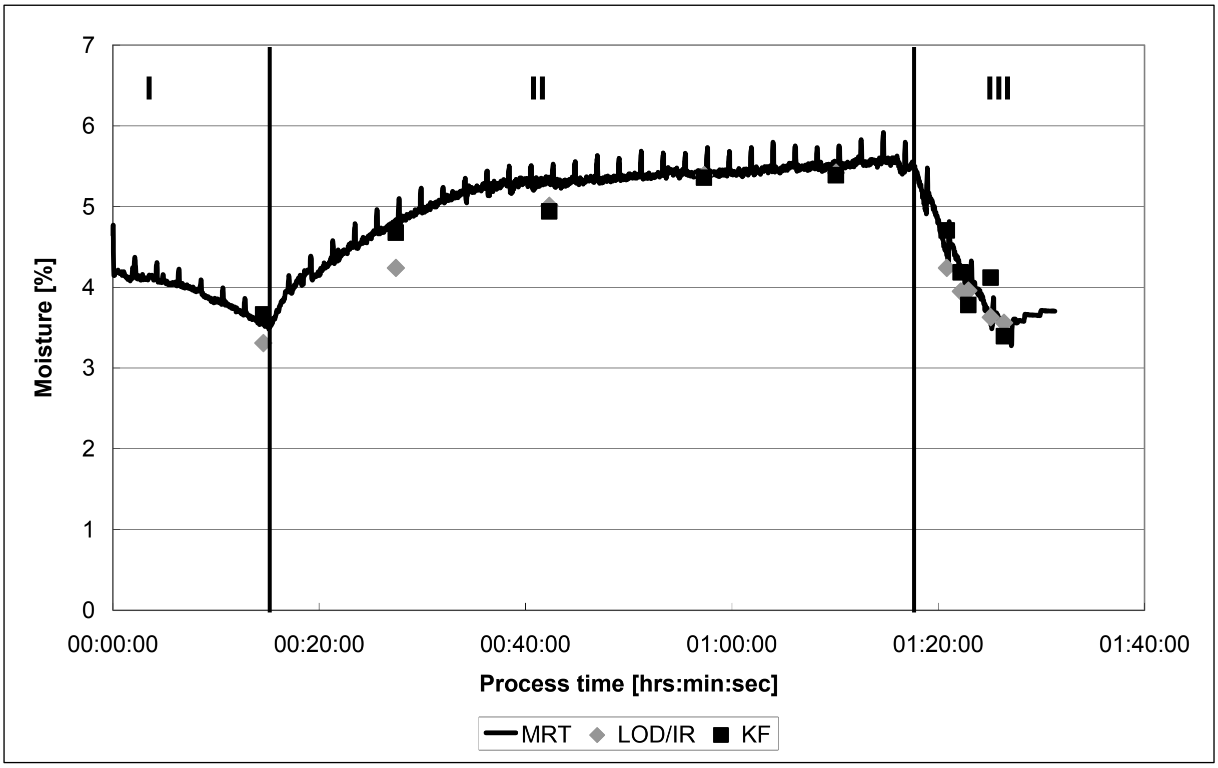

Fig. C-19: Moisture [%] of an example granule batch of product A throughout the entire wet granulation process (manufacturing device: WSG 60). I = pre-heating phase, II = spraying phase, III = drying phase.

Granulation processes can be divided into three phases: pre-heating, spraying and drying [Serno 2007].

This phenomenon is displayed in Figure C-19, which illustrates the moisture course of an exemple batch of product A throughout the entire process. Classification of the moisture values to the different granulation phases was possible for each time point.

Due to the increasing product temperature during the pre-heating phase, the moisture content decreased slightly from 4.2 % to 3.7 %. After reaching a product temperature of approximately 38°C, wet granulation was started (phase II, spraying), applying 17.4 kg aqueous solution of 7 % (m/m) povidone 90. During the spraying phase, the moisture increased slowly to a maximum value of nearly 5.6 %. As soon as the binder was completely applied, drying of the wet granules was started (phase III, drying).

Based on the results of previous studies (see chapter C 3), the drying process was not interrupted for periodically sampling and off-line moisture determination. Instead drying of the granules was performed continuously until the MRT sensor measured a moisture value meeting the required residual granule water content of < 3.8 %. The specified endpoint was reached after a drying time of approximately 12 minutes.

Additionally to in-line monitoring by MRT, samples were withdrawn at predefined time points throughout the entire granulation process. Their water content was determined by both reference methods, LOD/IR and KF.

Figure C-19 shows the moisture track measured in-line by MRT and the moisture values determined by KF and LOD/IR. Throughout the complete granulation process, a good agreement between the moisture measured in-line and off-line was achieved.

To get further information about the granulation courses and the reproducibility of the moisture monitoring various granule batches with the same composition were produced under comparable processing conditions.

The moisture courses of three example batches are presented in Figure C-20.

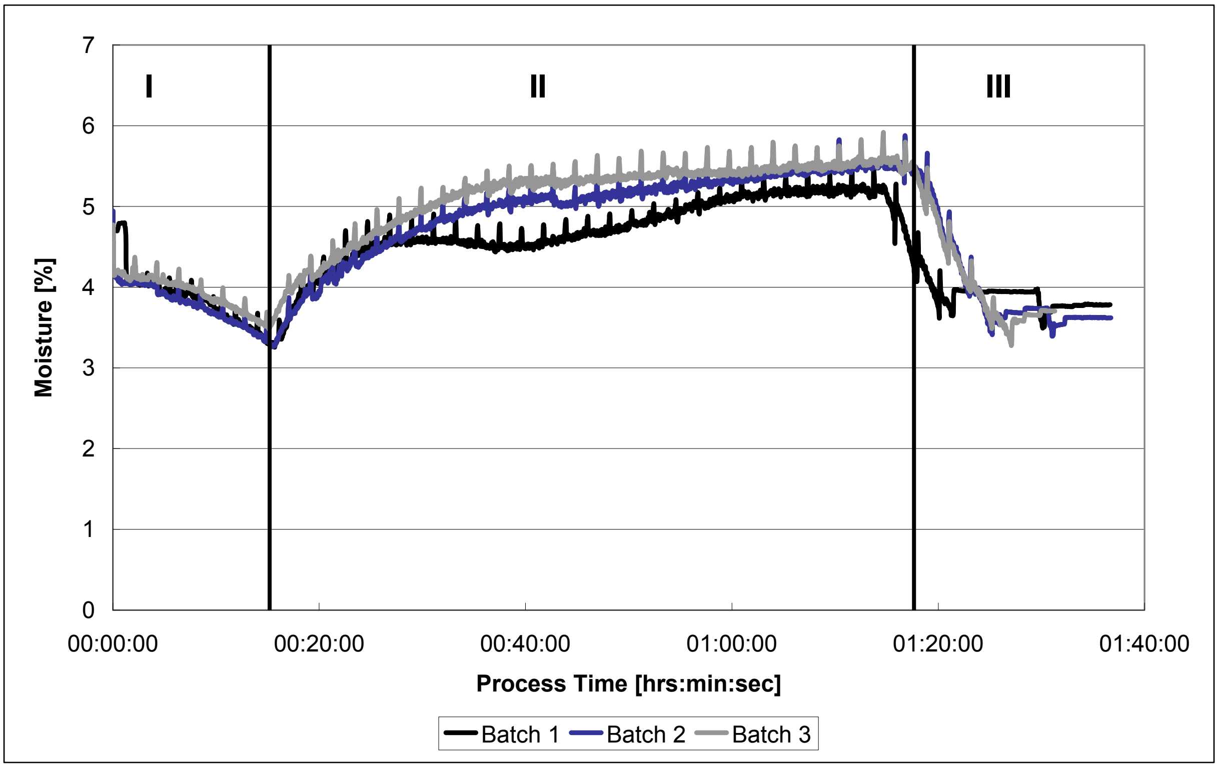

Fig. C-20: *Repeatability of moisture determination [%] by microwave resonance technology throughout the entire wet granulation process (manufacturing device: WSG 60). I = pre-heating phase, II = spraying phase, III = drying phase.*

All three batches showed a good agreement with each other indicating a reproducible, validated process. The moisture course of batch 2 was almost identical with the course of batch 3. During the production of the first granule batch, it was observed that the moisture was decreasing slightly after a process time of approximately 30 minutes. This effect was caused by a small increase of the product temperature. Therefore, the inlet air temperature was adjusted. In the following process course, the moisture of the first batch ran slightly beneath the moisture tracks of batch 2 and 3.

In all three batches, the initially granule water content was found to be approximately 4.6 %. During pre-heating and mixing of the powder blends, the moisture decreased to between 3.4 and 3.7 %. Due to applying the binder solution, the granule water content has increased slowly to approximately 5.7 % for batch 2 and 3. For batch 1 the maximum granule moisture measured was 5.3 %. The highest increase in moisture content was registered at the beginning of the spraying phase, it remained almost constant afterwards, indicating an optimal wet granulation process with equilibrated moisture values. In all cases, the maximum moisture value was measured at the end of the spraying phase.

Drying of the granules was performed continuously without any process interruptions for sampling and off-line moisture measurement. A reliable endpoint determination of the drying process was obtained for all three batches.

Slight differences of the moisture content of the three batches may be caused by the fact that the fluidized bed granulator WSG 60 operates with unconditioned inlet air.

Throughout the entire granulation process, it was possible to verify the phenomenon, which had been observed within previous studies (see chapter C 3). Due to the one chamber system of the fluidized bed granulator WSG 60, maxima in the granule moisture track were observed at regular intervals, which were caused by the periodically induced vibrations of the fine particle filters for cleaning purposes.

5.2 Temperature monitoring

Besides of the residual granule water content, the MRT sensor system also determines the product temperature and measures a value correlating with the product density. In order to measure the product temperature, a PT 100 thermo sensor is directly mounted under the senor's surface. It can be assumed that the recorded temperature correlates with the product temperature in the container of the granulator.

The moisture and temperature track of an example batch of product A is shown in Figure C-21.

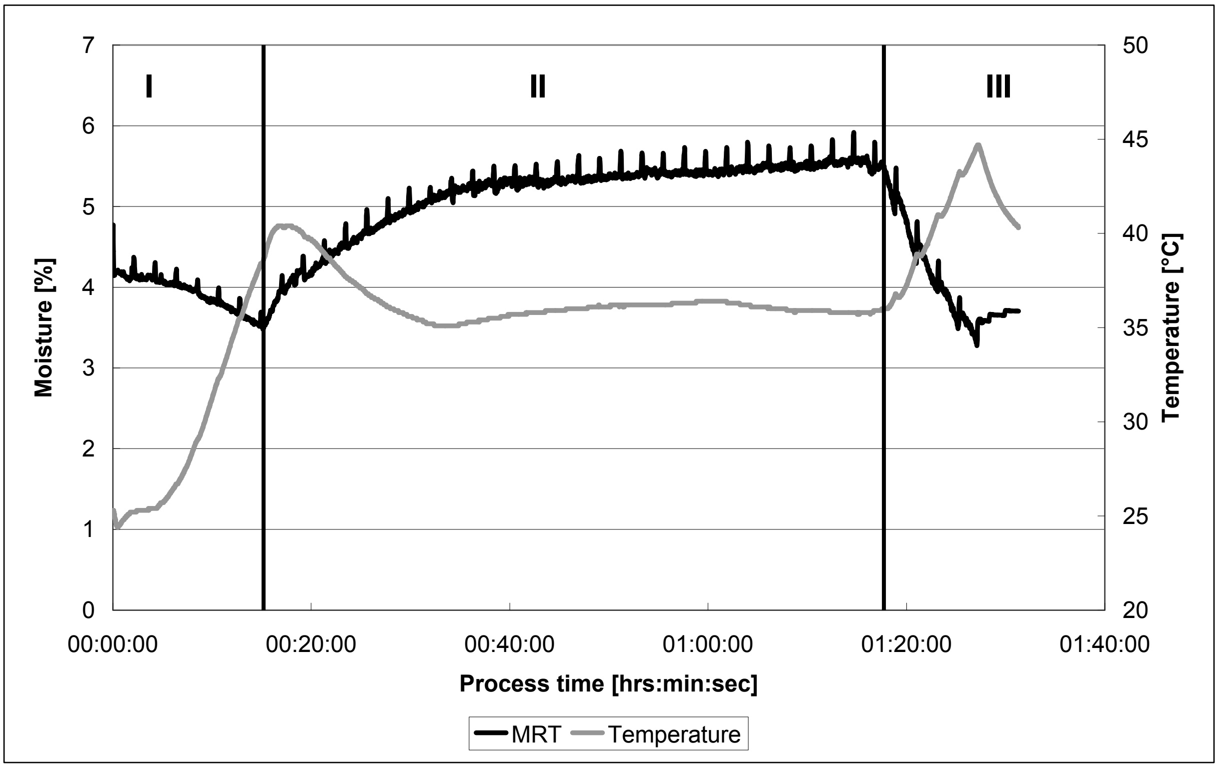

***Fig. C-21:** Moisture [%] and temperature [°C] tracks of one example granule batch of product A throughout the wet granulation process (manufacturing device: WSG 60). Continuous drying and endpoint determination based on MRT. I = pre-heating phase, II = spraying phase, III = drying phase.*

While the temperature increased within the preheating phase, the moisture decreased slightly from approximately 4.2 % to 3.7 %. After a product temperature of nearly 38 °C was reached, wet granulation was started applying the binder solution. Within the first two minutes of the spraying phase, the temperature increased to approximately 41 °C. In the following process course the moisture increased while the temperature decreased indicating the loss of energy by water vaporisation. After a process time of nearly 35 minutes an equilibrium was reached. At this point the moisture (5.4 – 5.6 %), as well as the temperature (35 – 36 °C), remained almost constant. The process parameters were adjusted ensuring that the amount of water used in the process was limited to the amount that could be discharged in the following.

Drying of the wet granules was started after the binder was completely applied. Within this process phase, the moisture and temperature curves changed complementary. The more the temperature increased, the more the water content of the granules decreased. As described previously the drying process ran without interruptions due to the use of the MRT sensor. The in-line monitoring of granule moisture enabled the continuous identification of the specified drying endpoint.

The temperature curve reached its maximum, in this case 45 °C, as soon as the drying endpoint was reached (Figure C-21). As well as the granule water content, the in-line monitoring of the product temperature emphasised an additional useful parameter for the determination of the drying endpoint.

The moisture and temperature tracks of one further batch of product A are illustrated in Figure C-22. During this granulation process, the MRT sensor was only used for information purposes and not for the identification of the drying endpoint. Consequently the process was interrupted at predefined time points throughout the drying phase for sampling and off-line moisture determination by LOD/IR. During these process interruptions, each for a few minutes, the fluidisation was stopped. Throughout the analysis time, the sensor measured a constant moisture value that can be seen in Figure C-22 as a moisture plateau.

By measuring the temperature simultaneously, interesting effects of the interruptions were observed. While the product temperature decreased during the first stop, the following two process interruptions led to an increasing temperature. Similar fluctuations of the product temperature during subsequent stops of the drying process were observed. Such uncontrollable fluctuations of a product parameter provide a risk for the product quality. It is no longer possible to guarantee that product quality at the point of sampling corresponds with product properties at the end of the process interruption. An increasing product temperature during the process stops may lead to further irregular drying of the granules due to the absence of fluidisation. In contrast, a decreasing product temperature may lead to a re-moistening of the granules. Consequently, the risk of lump formation increases. Furthermore, the temperature decreased throughout the entire drying process with increasing numbers of process interruptions. This could lead to elongated drying process times and expose the granules for longer to the stressful drying conditions.

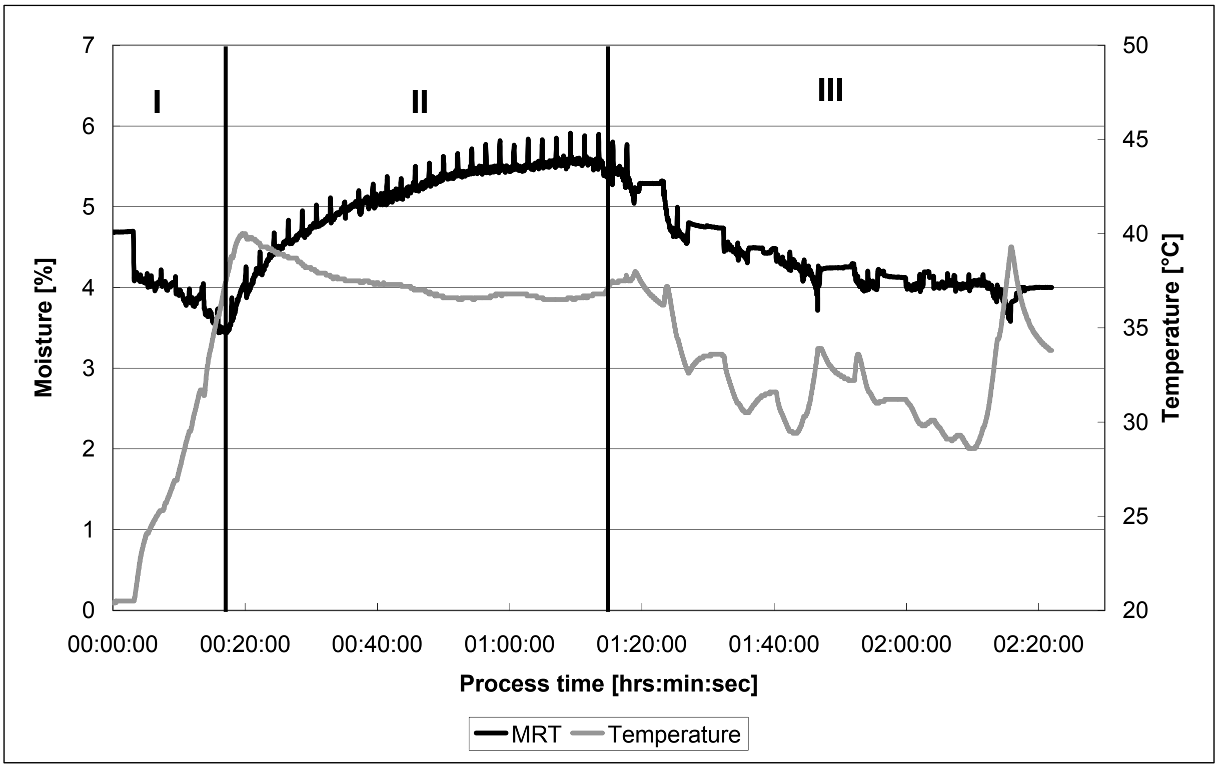

Fig. C-22: *Moisture [%] and temperature [°C] track of one granule batch of product A throughout the entire fluidized bed granulation process (manufacturing device: WSG 60). Discontinuous drying in the terminal phase due to sampling for off-line moisture determination. I = pre-heating phase, II = spraying phase, III = drying phase*

5.3 Conclusion

The microwave resonance sensor was proven to be a valuable tool for the in-line moisture monitoring of crystal-water-free granules throughout the entire wet granulation process.

A reliable determination of the drying endpoint and reproducible moisture monitoring over the complete process was obtained. A strong correlation between the MRT moisture and the results of the reference methods was found throughout the entire granulation process.

Simultaneous monitoring of the moisture and temperature throughout the granulation process was found to be a helpful tool for process control as well as ensuring product quality and improve process understanding. In addition it allowed the identification of the drying endpoint and to monitor batch-to-batch process variations. In combination with moisture monitoring, a detailed insight into the process course was gained.

6 Monitoring of the entire wet granulation process of crystal-water-containing granules

For the determination of the drying endpoint of crystal-water-containing granules the MRT sensor system was proved to be a valuable tool (see chapter C 4). Within this study it was investigated if the MRT sensor is also suitable for the control of the entire wet granulation process of crystal-water-containing granules.

6.1 Moisture monitoring

A granule batch of product D consisting of ≤ 1 % of an estrogen (group II), ≤ 1 % of an API of group III, 72 % α-Lactose monohydrate, 26 % partially pregelatinized maize starch and ≤ 2 % of substance PW02 was produced under GMP conditions in the fluidized bed granulator WSG 60. The product requires extremely low moisture, ideally < 3 %. Wet granulation was performed applying a 9.4 % aqueous solution of povidone 30. For comparing MRT results with both reference methods, LOD/IR and KF, samples were withdrawn at predefined time points and analyzed off-line.

In Figure C-23, the moisture track of the granule batch recorded in-line by the MRT sensor system and the results of the reference methods are displayed.

As both APIs were sensitive to moisture the granulation process had to be performed at a low moisture level. Parameter setting had to be chosen accordingly (see chapter F 2.1.1). To meet these requirements, the main focus was on moisture control by MRT throughout the entire wet granulation process.

Subsequent to the preheating phase, the binder solution was applied. This led to an increase of the moisture content of approximately 1 %, from 1.5 % to about 2.5 %, within the first 15 minutes of spraying. Afterwards the water content settled down to a range of 2.5 to 2.7 %. The granules were dried until reaching a residual water content of approximately 2 %. Throughout the entire granulation process the moisture content was under 3 %. As the required residual granule water content was specified in the range of 1 to 3 % the drying process was quite short.

As to be seen in Figure C-23, the curve progressions of the three methods used for water determination, MRT, LOD/IR and KF, were quite similar. Although the sensor system was used in the default setting without specific calibration a good correlation between MRT and LOD/IR moisture measurement was observed throughout the entire granulation process. Comparing both moisture tracks an interesting phenomenon was observed. The moisture measured in-line was slightly lower than the results of LOD/IR throughout the entire process. However, it would be expected that the same, or slightly higher, moisture contents are measured using the microwave resonance sensor. The reason for this is that microwaves permeate the whole product, while LOD/IR only detects water slightly bounded on granule's surface. In order to investigate this effect in more detail, further granulation processes were performed under experimental conditions (see chapter C 9).

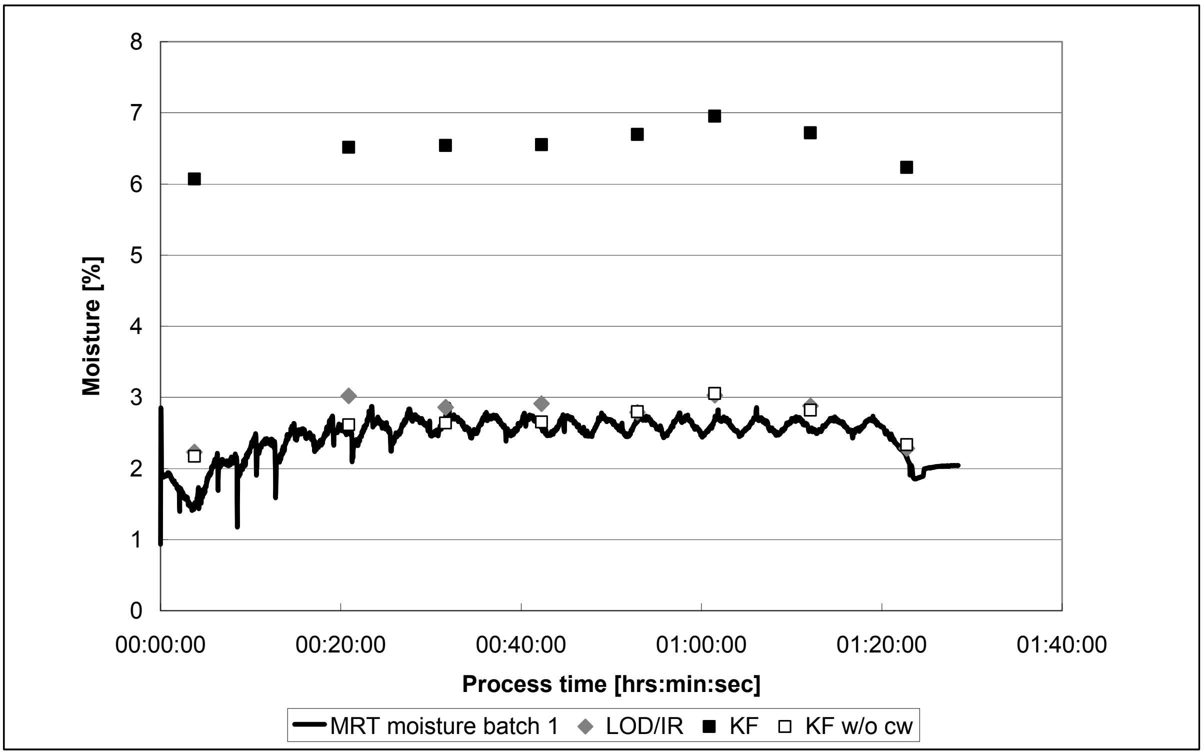

Fig. C-23: Moisture [%] course of an example batch of the crystal-water-containing product D determined in-line by MRT and off-line by LOD/IR and KF (manufacturing device: WSG 60).

As described above, the curve progressions of MRT, LOD/IR and KF were quite similar. However, KF detects all water types including crystal-water. Neither LOD/IR nor MRT are able to detect this water type under the present conditions. As expected, the results of KF were found to considerably exceed the other methods (Figure C-22). As the fraction of crystal-water has no direct influence on product properties during the granulation process, it was neglected for the moisture monitoring throughout the process. In order to compare the results of all three methods with each other, the fraction of crystal-water contained in this product (approximately 3.9 %) was subtracted from the original KF results. The resulting corrected KF results were found to be nearly identical with the results of water determination by LOD/IR. Furthermore, a good correlation to the moisture recorded in-line by MRT was obtained.

To investigate the reproducibility of moisture monitoring of crystal-water-containing granules by MRT, two further batches of product D were produced under comparable conditions.
As Figure C-24 shows, the three moisture courses recorded in-line by MRT showed a good agreement among each other. This indicates a validated process as well as a reproducible moisture measurement by MRT.

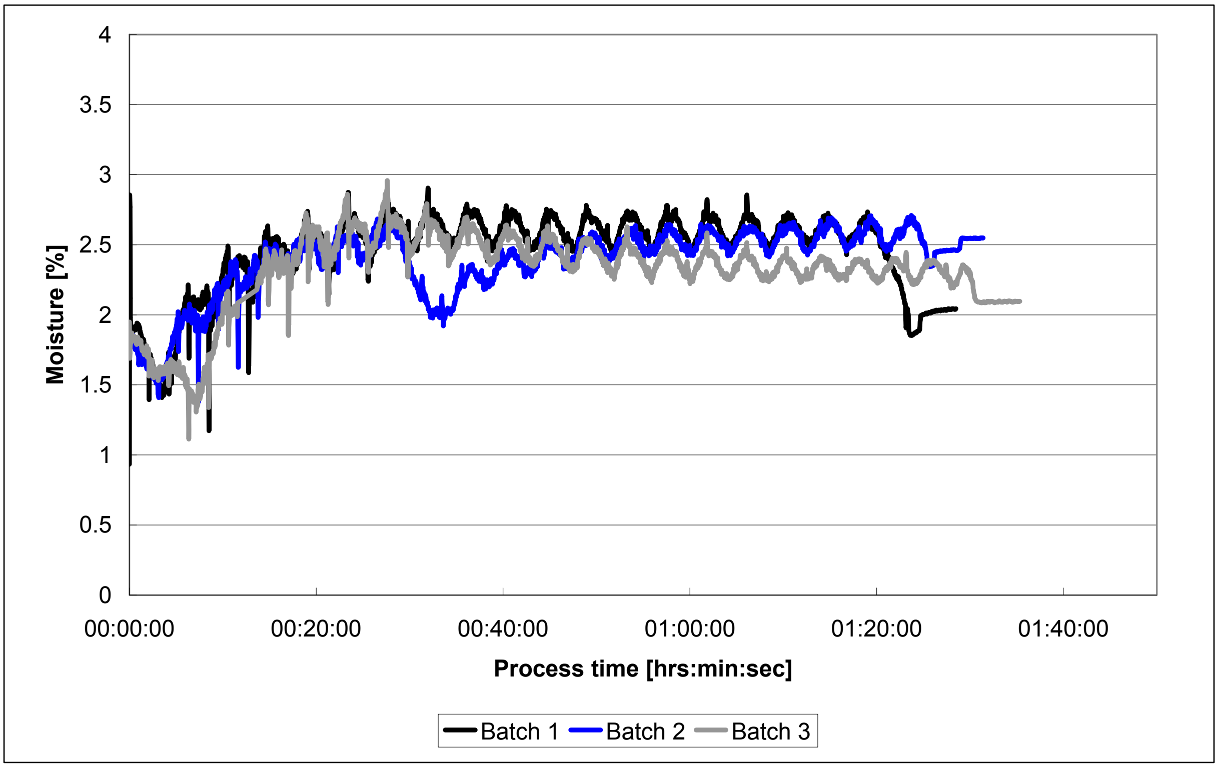

Fig. C-24: *Moisture [%] tracks of three granule batches of product D produced under comparable process conditions (manufacturing device: WSG 60).*

During the granulation process of a second batch with the same composition, a decrease in moisture content of approximately 0.8 % was observed after a process time of about 28 min. This change was caused by an increase in the product temperature of 5°C. Subsequently, an adjustment of the inlet air temperature was performed to ensure an increase of the moisture to the desired level. To what extent this deviating moisture track impacted compression behaviour was investigated subsequently (see chapter C 7).

Furthermore, the granulation process of the second granule batch provided one further special feature. For the granulation process of the first and third batches, all solids were located in the product container of the fluidized bed apparatus and spraying was performed by applying an aqueous solution of povidone 30. In contrast for the second batch, both active pharmaceutical ingredients were suspended in the aqueous granulating fluid leading to a solid fraction of approximately 1 %. Thus, spraying was performed by applying a suspension instead of the former practice of applying a solution. It is noteworthy that the type of granulating fluid used was not observed to have an influence on the moisture measurement.

With the aim to verify the use of the MRT sensor system for in-line moisture monitoring, two further granule batches of a crystal-water-containing product were produced as described below.

Powder blends of product C, consisting of 33 % MCC and 67 % α-Lactose monohydrate were granulated in the fluidized bed granulator GPCG 15 under comparable conditions. Granulation conditions can be found in the chapter F 2.1.1. As granulating fluid, a 10 % (m/m) aqueous solution of povidone 90 was applied. To compare MRT results with a reference method, the samples were withdrawn throughout the process and analyzed off-line by LOD/IR. The granulation process of the first granule batch proceeded as expected and the typical three phases of a wet granulation process were observed (Figure C-25). By pre-heating (I) the powder blend the moisture decreased from approximately 1.7 % to 0.7 %. Within the spraying phase (II) the moisture increased due to the application of the binder solution, until reaching a maximum moisture content of nearly 4.9 %. During the drying (III) of the wet granules, the moisture decreased until the predefined endpoint was reached. Throughout the entire process a good correlation between the moisture values measured in-line and the results of the off-line water determination by LOD/IR was obtained (Figure C-25).

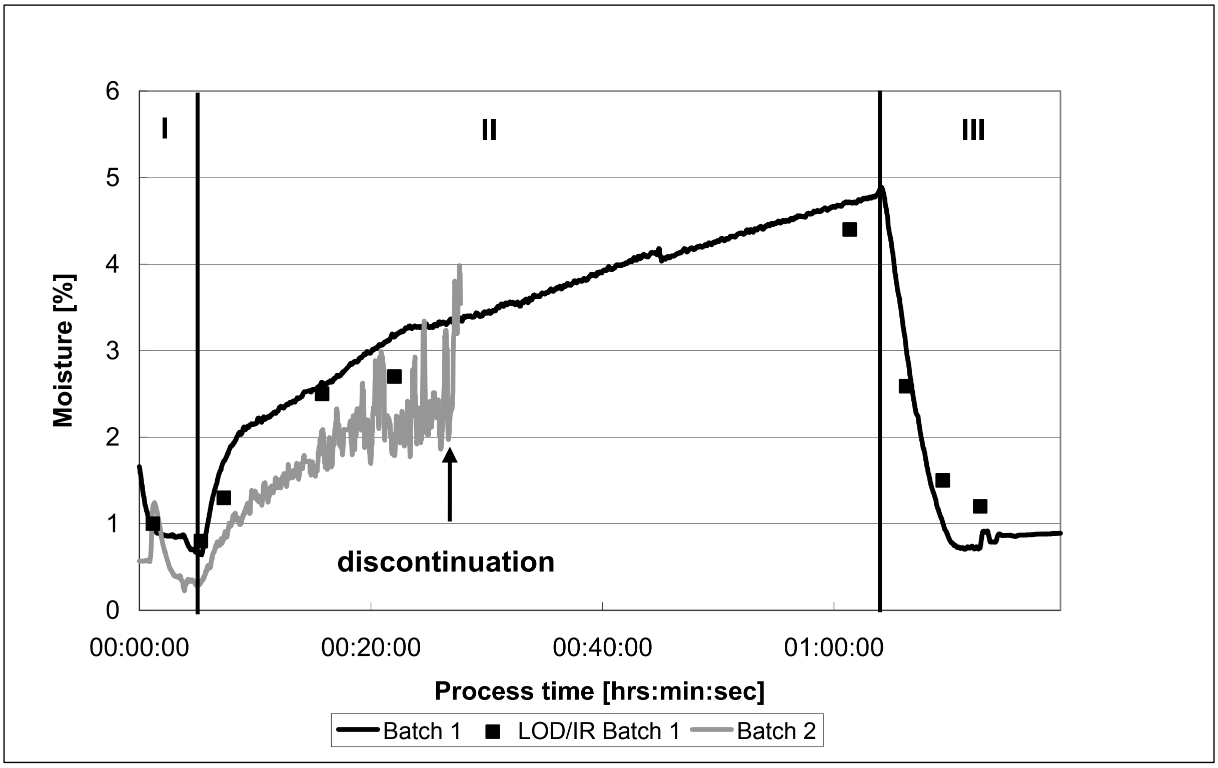

Fig. C-25: Comparison of moisture [%] tracks of both granule batches of product C. Batch 1 with regular granulation course and corresponding LOD/IR results and batch 2 with deviating moisture course due to a system failure (manufacturing device: GPCG 15). I = pre-heating, II = spraying, III = drying phase

For the second granule batch, the preheating phase proceeded as described before. Due to the increasing product temperature, the moisture decreased about 1 %. After a few minutes of applying the binder solution, fluctuations of the moisture course were observed.

In the following process course, these fluctuations led to increasing maxima of the granule water content. In comparison to the first granule batch, a considerably differing moisture track was recorded (Figure C-25). While the granule water content of the first batch increased uniformly when applying the binder, the moisture track of the second batch got more and more irregular.

In order to identify the reason for the differing moisture track it was decided to discontinue the process after a process time of approximately 27 minutes (Figure C-25). During the following inspection of the granulator, a breakdown of the spraying air supply was identified to be responsible for the deviating moisture course of the second batch. This failure led to a trickling of the binder solution directly into the fluidized bed, causing a local overwetting of the solid particles, an irregular moisture distribution, and formation of lumps.

Being unrecognized during GMP production, such a system failure would lead to considerable losses of product quality. In the worst case, such a failure would necessitate the rejection of the respective batch. This would be associated with considerable financial losses. Accordingly, the use of the MRT sensor system for in-line moisture control is not only attended with benefits for product quality or process acceleration. In fact, the use of this in-line monitoring tool allows the identification of possible problems throughout the entire granulation process. Thus, an intervention at an early stage becomes possible. Final product quality is ensured.

6.2 Density monitoring

As well as the determination of moisture content and product temperature, the microwave resonance sensor enables the study of the density track (see chapter C 1). However, no direct density value is measured. In fact a signal which correlates with product density is recorded in-line. Thus, valuable information about the granulation process are available.

The density and moisture tracks of the first granule batch of product D (for detailed information see chapter C 6.1) are displayed in Figure C-26.

Within the first 30 minutes of the process, considerable fluctuations of the density were observed. During the preheating and at the beginning of the spraying phase, an intensive blending of the individual ingredients was performed. By applying the binder solution, particle growth was initiated due to the agglomeration of individual powder particles to coarser granules. These normal effects give an explanation for the strong fluctuation of the density at the beginning of the granulation process. During the spraying phase, the fluctuations of the particle density decreased until they settled down to a nearly constant value after a process time of approximately 1 hour.

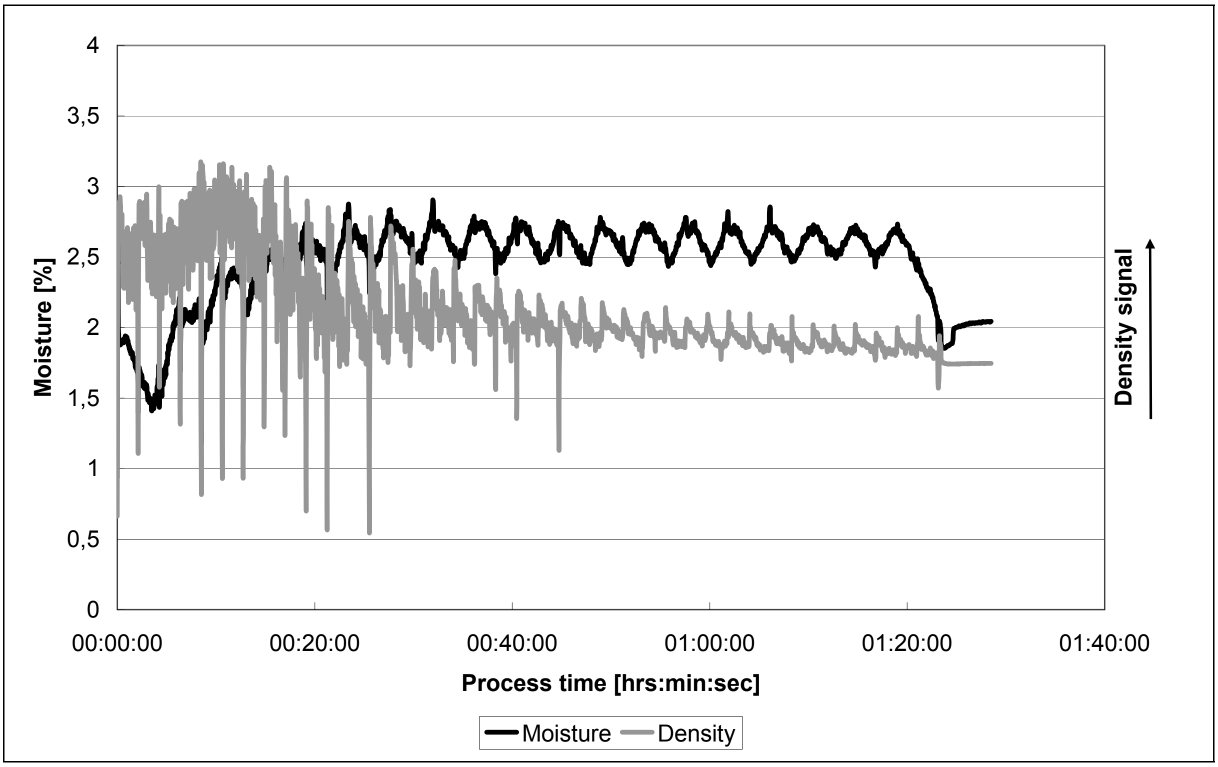

Fig. C-26: *Moisture track [%] and density signal of one granule batch of product D recorded by the MRT sensor system (manufacturing device: WSG 60).*

It is obvious that the in-line monitoring of a signal correlating with product density is a valuable tool for rating the course of a wet granulation process. While distinctive fluctuations in the density track indicate ongoing blending procedures and granule growth, nearly uniform density signals indicate a homogeneous and completed granulation process.

Furthermore, a phenomenon was observed which was already noticed within previous granulation processes for the moisture monitoring by MRT (see chapter C 3, C 4). At regular intervals maxima and distinctive minima in the density track were observed. An exact correlation of the time points of the vibrations due to the cleaning process and fluctuations in the moisture and density curves were found. Obviously, the vibrations of the fine particle filters have an impact on the granulation process by continuously detaching fines from the fluidized bed to the filters and discharging them to the bed periodically.

In Figure C-27 the recorded density signals of the three batches of product D (see chapter C 6.1) are plotted against the process time.

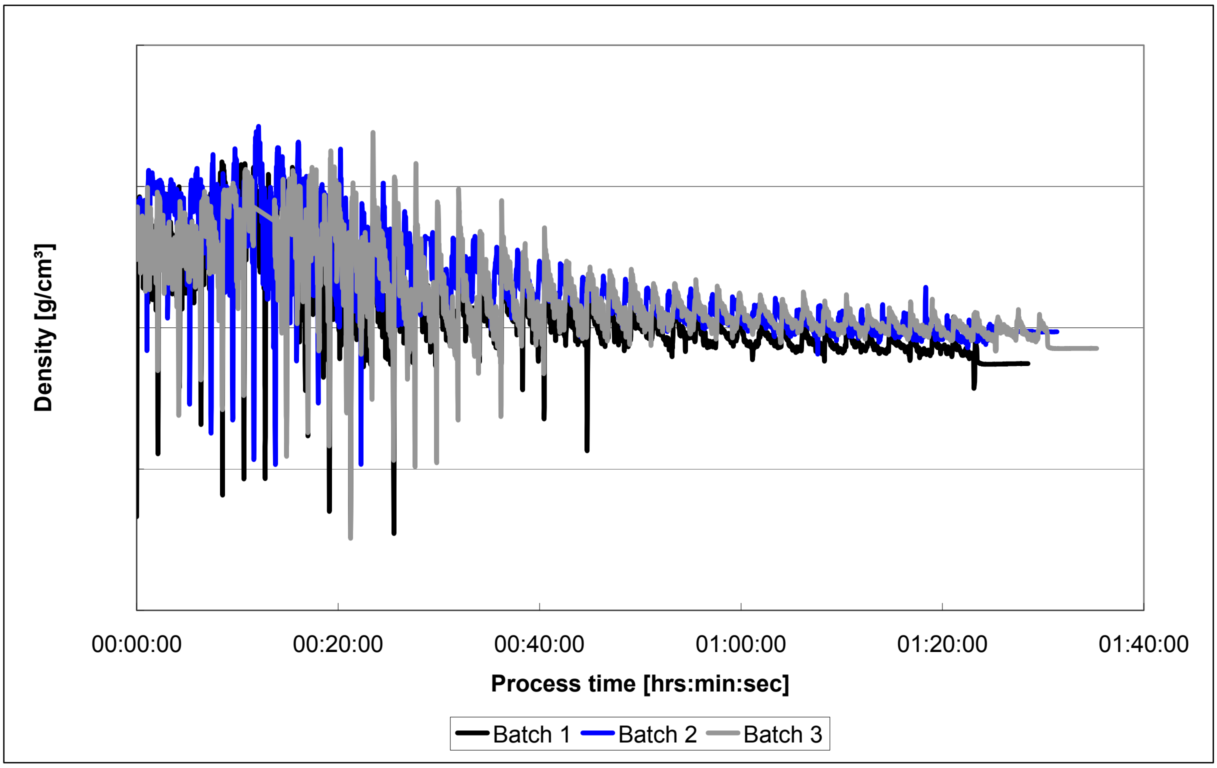

Fig. C-27: *Density tracks of three batches of product D recorded in-line by MRT (manufacturing device: WSG 60).*

Nearly identical curve progressions of the density tracks of the three batches were observed. During the first 30 minutes of the granulation process, considerable fluctuations of the signals correlating with product density were detected. Following this, the process density fluctuations decreased. In all three batches the density settled down to an nearly constant value, indicating the end of a homogeneous and well validated granulation process. By using the microwave resonance sensor for the in-line monitoring of the MRT signal correlating with product density comparable density tracks were recorded for the three batches.

6.3 Moisture and density measurement by MRT of various products

The granulation processes of two crystal-water-containing products are described in detail in chapter 6.1. However, granulation processes of many various products with different compositions were monitored within this study using the MRT sensor system. A selection of monitored processes is given in the following paragraphs. All products have in common that the contained APIs are sensitive to high moisture contents. Thus granulation had to be performed at low moisture levels.

Granulation conditions can be found in chapter F 2.1.1.

Figure C-28 shows the moisture tracks of two batches of product E. Their composition was ≤ 1 % of an estrogen (group II), ≤ 3 % of an API of group III, 67 % α-Lactose monohydrate and 31 % partially pregelatinized maize starch (PPMS). As granulation was performed under GMP conditions, granulation parameters were specified exactly. Therefore, a batch to batch comparison was possible.

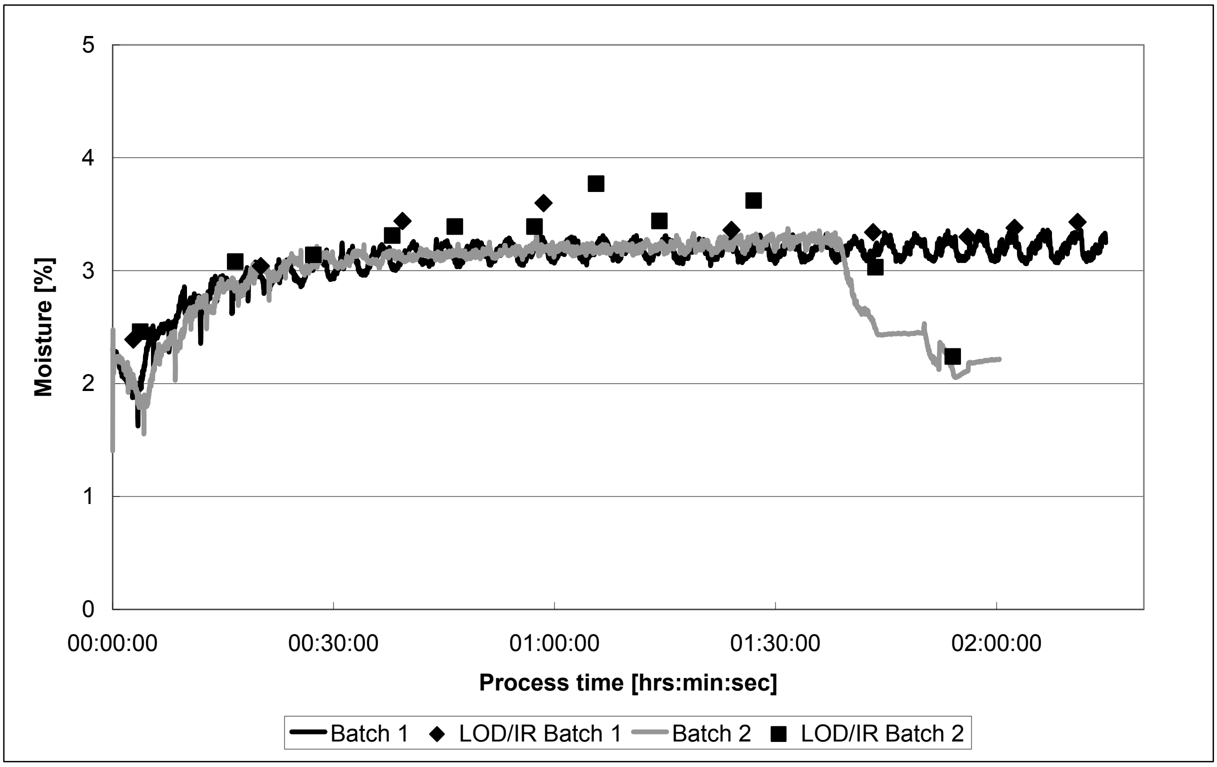

Fig. C-28: *Moisture [%] tracks of two example batches of product E. For batch 1 the APIs were suspended in the granulating fluid. For the second batch the APIs were contained in the solid fraction in the granulator (manufacturing device: WSG 60).*

In addition to the in-line moisture measurement by MRT, the water content was determined off-line by LOD/IR. Both methods showed a good agreement throughout the entire process.

For batch 1 both APIs were suspended in approximately 14 kg purified water. Afterwards the suspension was incorporated in the granulating fluid, which was 27.5 kg of an aqueous solution of approximately 9 % (m/m) of povidone 30 and 0.3 % of sodium edetat. The resulting granulating suspension contained a solid fraction of nearly 5 %.

For the second granule batch the APIs were incorporated in the solid fraction in the fluidized bed granulator. Spraying was performed applying 27.5 kg of a 9 % (m/m) aqueous solution of povidone 30 and 0.3 % sodium edetat.

Figure C-28 shows that the moisture courses of both batches are nearly identical. Due to a larger amount of granulating fluid being applied, the process of the first batch was lengthened accordingly (after a process time of nearly 135 min the MRT monitoring was stopped).

Obviously, the character of the granulating fluid, solution or suspension, has no impact on the process course and moisture measurement by MRT. The observation that a suspension with a solid fraction of 1 % (see chapter 6.1) has no influence on moisture measurement by MRT could be verified by applying a binder suspension with approximately 5 % solids.

Additionally, the moisture and the density tracks of both batches were recorded by the MRT sensor system (see Figure C-29). Both curves are nearly identical. The observations of nearly constant density signals at the end of the process (see chapter 6.2) were confirmed. At the beginning of the granulation process considerable fluctuations in the density tracks were monitored. In the following course these fluctuations decreased more until the density signals became nearly constant.

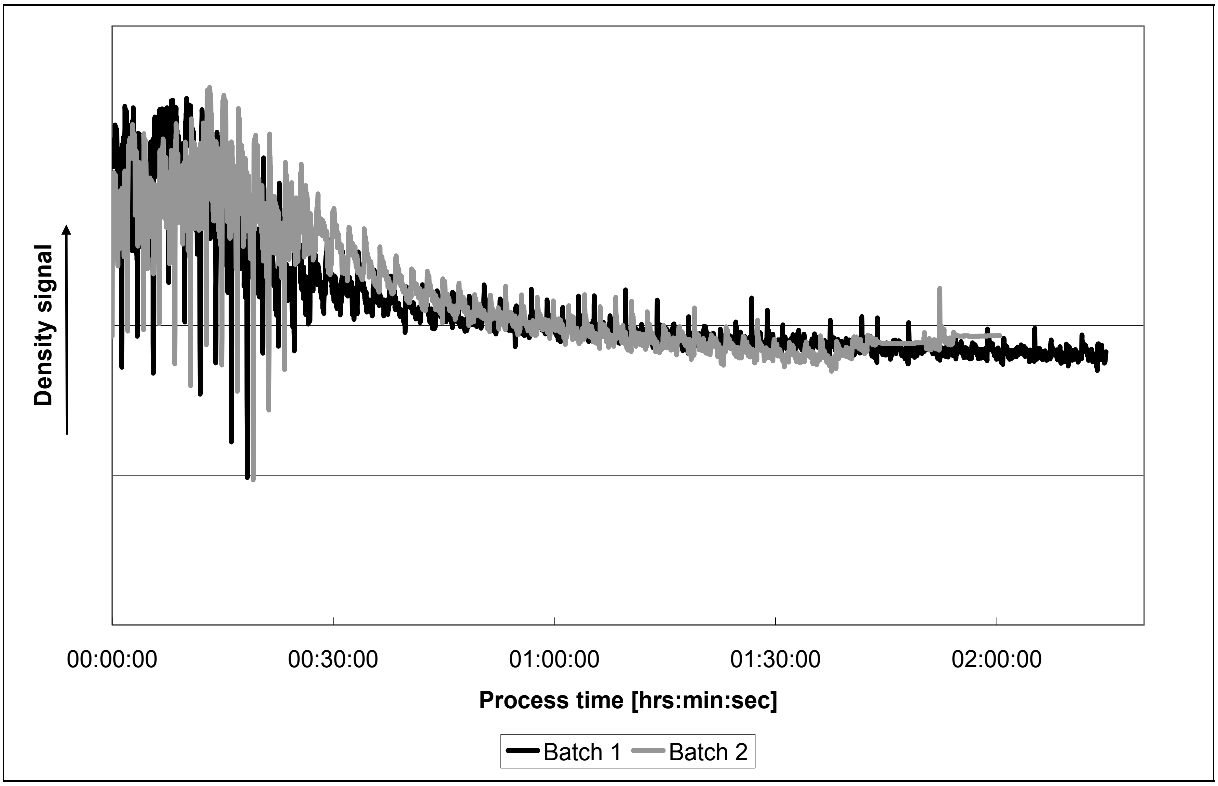

Fig. C-29*: Density tracks recorded by the MRT sensor of two granule batches of product E (manufacturing device: WSG 60).*

The moisture tracks of three batches of product F are displayed in Figure C-30. Batch 1 and 2 consisted of one API of group II (≤ 2 %), 16 % MCC, 72 % α-Lactose monohydrate, 10 % PPMS and 0.1 % Ascorbic acid. In batch 3 the proportion of MCC was replaced by PPMS. Thus, the fraction of PPMS for the third batch was 26 % with regard to the total mass of the solids. Other ingredients were contained in the same proportions as batches 1 and 2. Wet granulation was performed in all cases by applying approximately 31 kg of an 8 % (m/m) aqueous solution of povidone 30. Additionally the granulating fluid contained Tartrazine (E102) as a colouring agent in a concentration of 0.2 %.

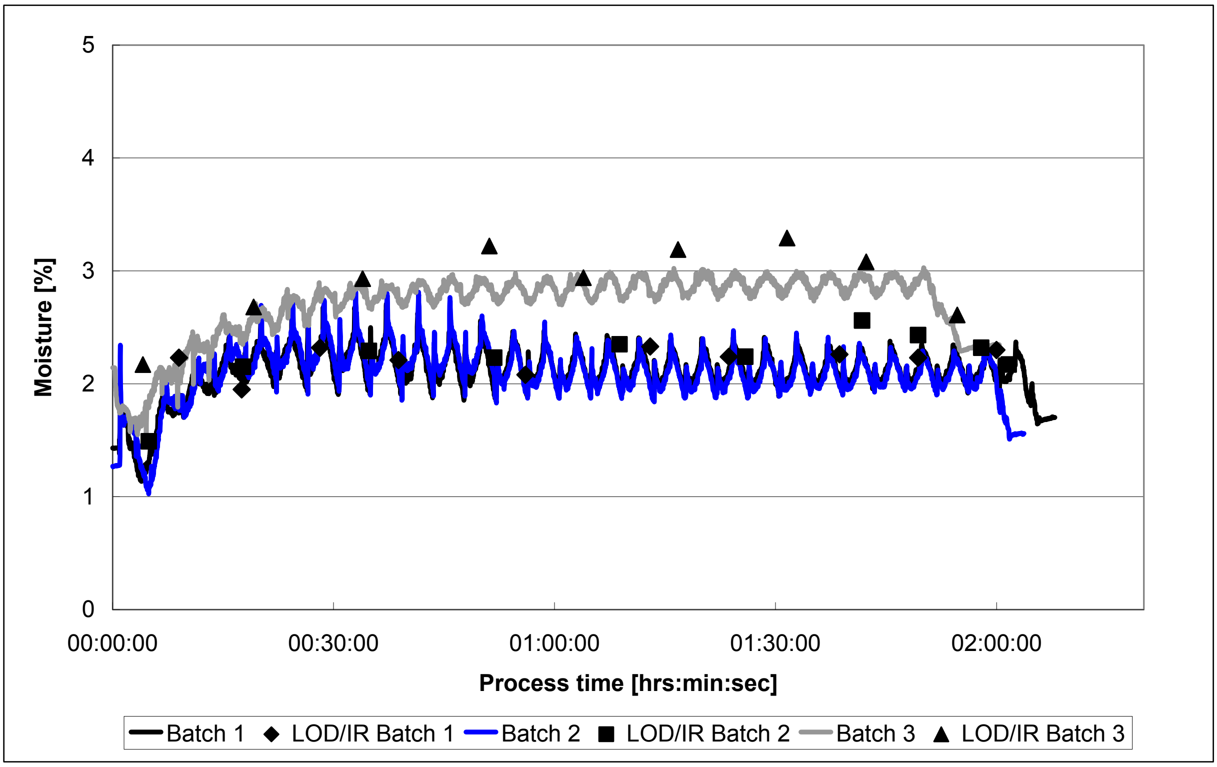

Fig. C-30: *Moisture [%] tracks recorded in-line by MRT and off-line by LOD/IR of three batches of product F (manufacturing device : WSG 60)*

While the moisture tracks of batch 1 and 2 were nearly identical, the moisture content of the third granule batch was approximately 0.8 % higher. This may be due the modified composition of batch 3 with PPMS. In addition the granulating fluid of the third batch was applied with a slightly higher spraying rate, 320 g/min instead of 280-300 g/min.

As it was reported that the colour of the product does not affect the moisture measurement by MRT [Wernecke 2003], but influences spectroscopic methods such as NIR, it was of particular interest whether this statement concerning MRT measurement could be verified.

Therefore, the moisture values recorded in-line were compared with the results of the off-line reference method LOD/IR. All measured values were in good agreement throughout the entire wet granulation process (Figure C-30). An effect on MRT moisture measurement by applying a coloured granulating fluid was not observed.

In Figure C-31, the tracks of the density signals of the three batches of product F recorded by the MRT sensor system are plotted against the process time. In addition to a higher moisture course, the density of batch 3 was found to exceed batch 1 and 2 as well.

The impacts of these differences between the three batches on the subsequent tabletting process were investigated in the following (see chapter C-7).

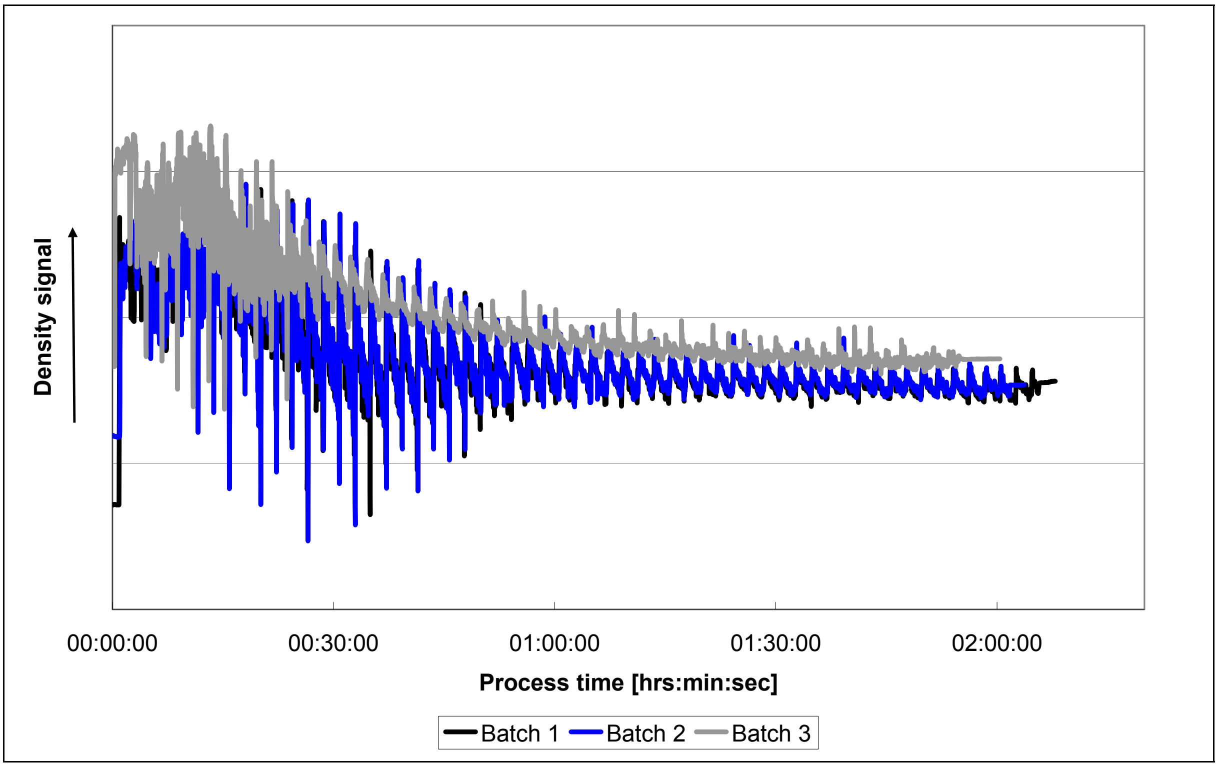

Fig. C31: *Density tracks recorded in-line by MRT three batches of product F (manufacturing device: WSG 60).*

In the following, the moisture and density tracks of two further products are illustrated. The compositions of both products were similar. Product G (Figure C-32 and C-33) consists of one API of group II (≤ 1 %), one API of group III (≤ 3 %), 67 % α-Lactose monohydrate and 30 % PPMS.

In product H (Figure C-34 and C-35) the API of group III was replaced by another API of group III resulting in a slightly differing mass distribution of excipients: one API of group II (≤ 1 %), one API of group III (≤ 1%), 73 % α-Lactose monohydrate and 26 % PPMS. Wet granulation was performed in both cases applying approximately 25 kg of an aqueous solution of 11 % povidone 30.

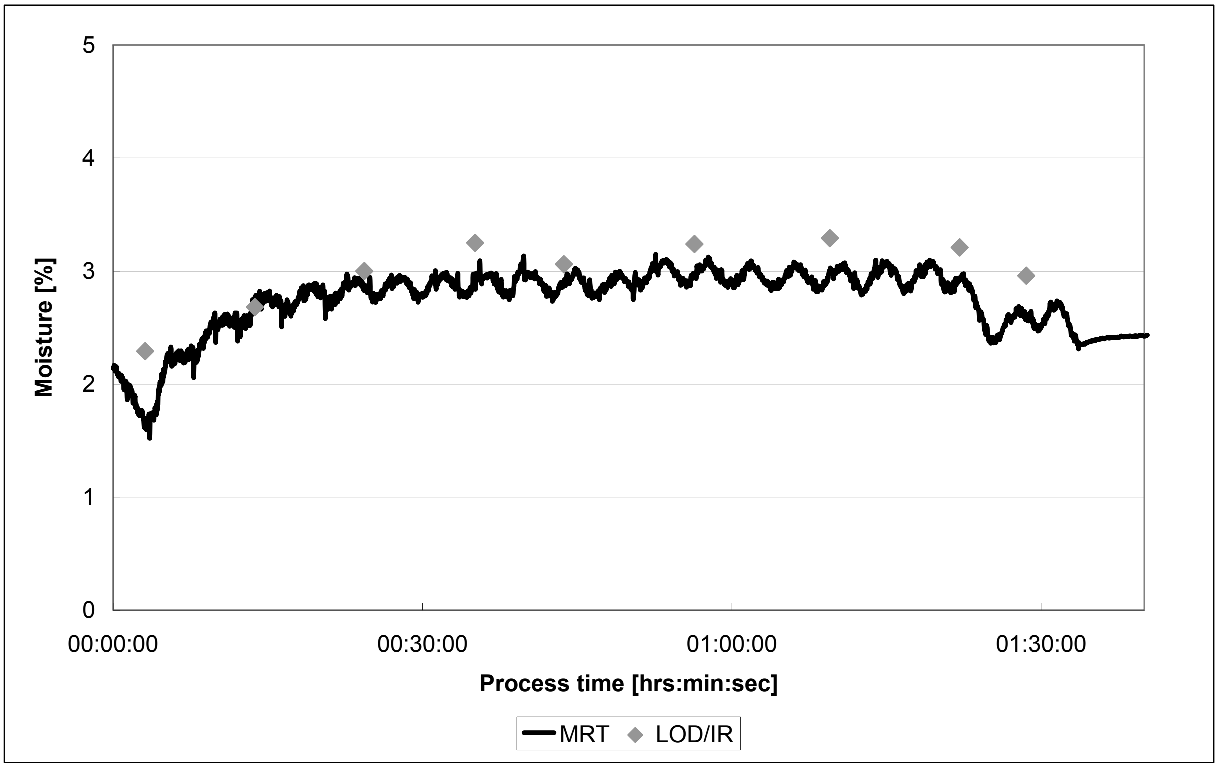

Fig. C-32: *Moisture [%] tracks of product G recorded in-line by MRT and off-line by LOD/IR (manufacturing device: WSG 60).*

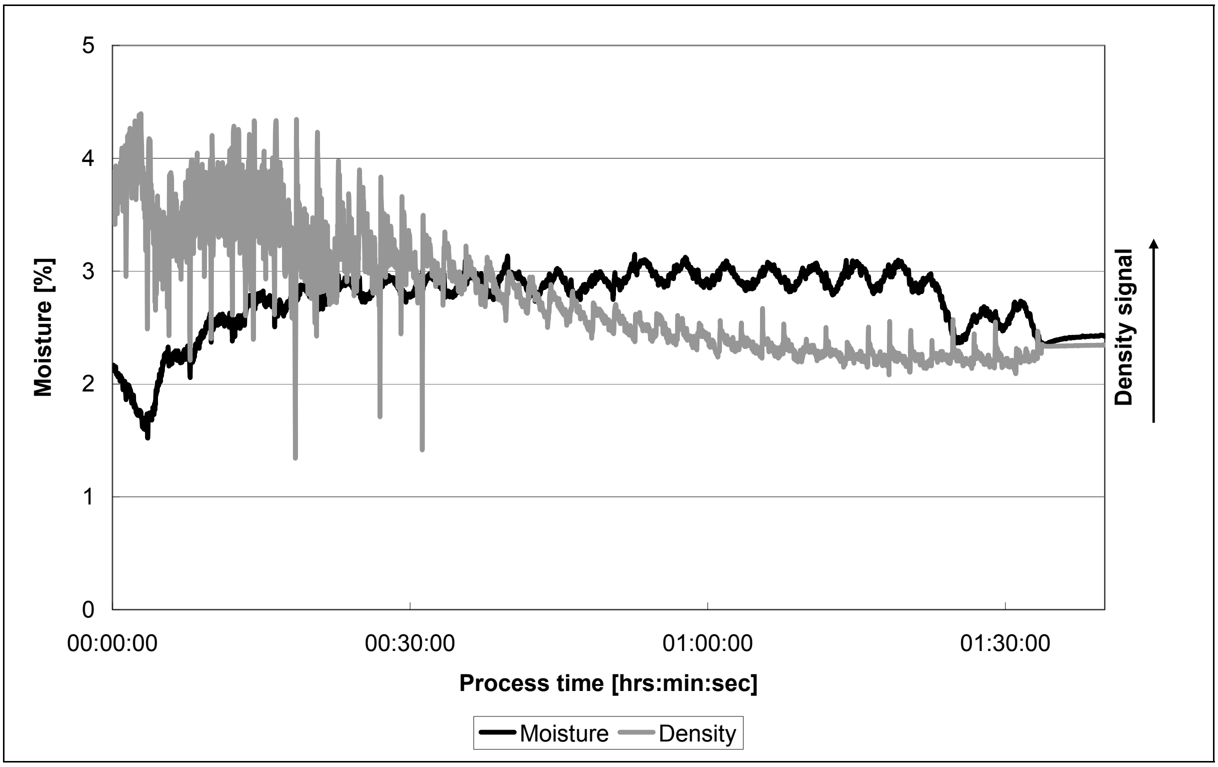

Fig. C-33: *Moisture [%] and density tracks of product G recorded in-line using the MRT sensor system (manufacturing device: WSG 60).*

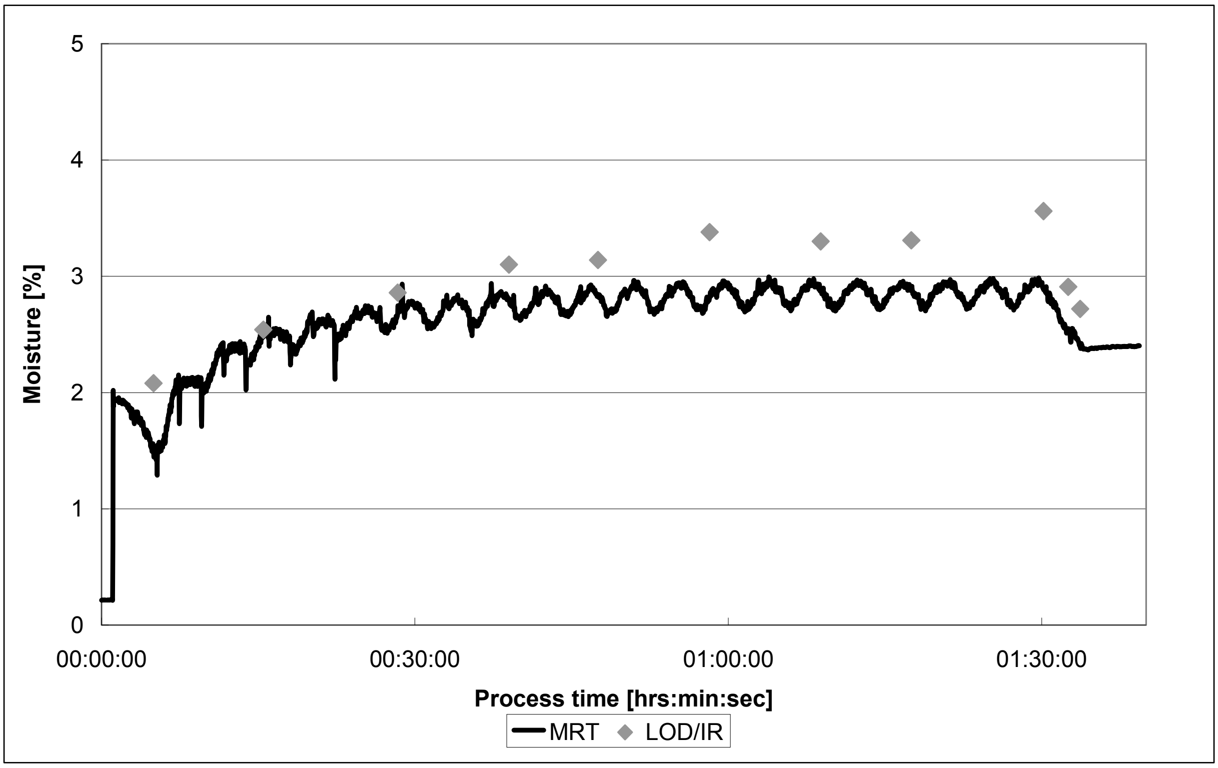

Fig. C-34: *Moisture [%] of one example batch of product H recorded in-line by MRT and off-line by LOD/IR (manufacturing device: WSG 60).*

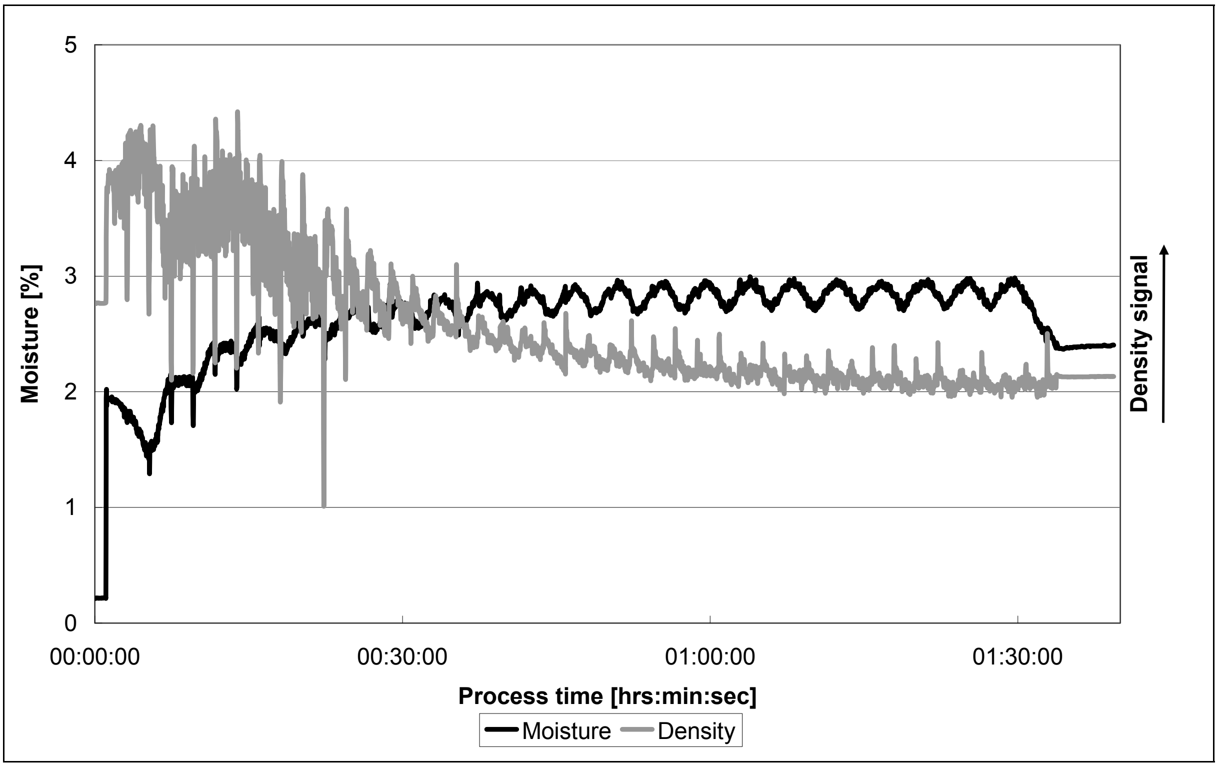

Fig. C-35: *Moisture [%] and density track of one example batch of product H recorded in-line by MRT (manufacturing device: WSG 60).*

It was observed that the moisture tracks (Figures C-32 and C-34) and the density courses (Figures C-33 and C-35) showed nearly identical curve progressions. The moisture tracks of both products recorded by the MRT sensor system correlated well with the results of the reference method LOD/IR.

It became obvious that slight modifications of this basic formulation have no direct influence on moisture determination by MRT.

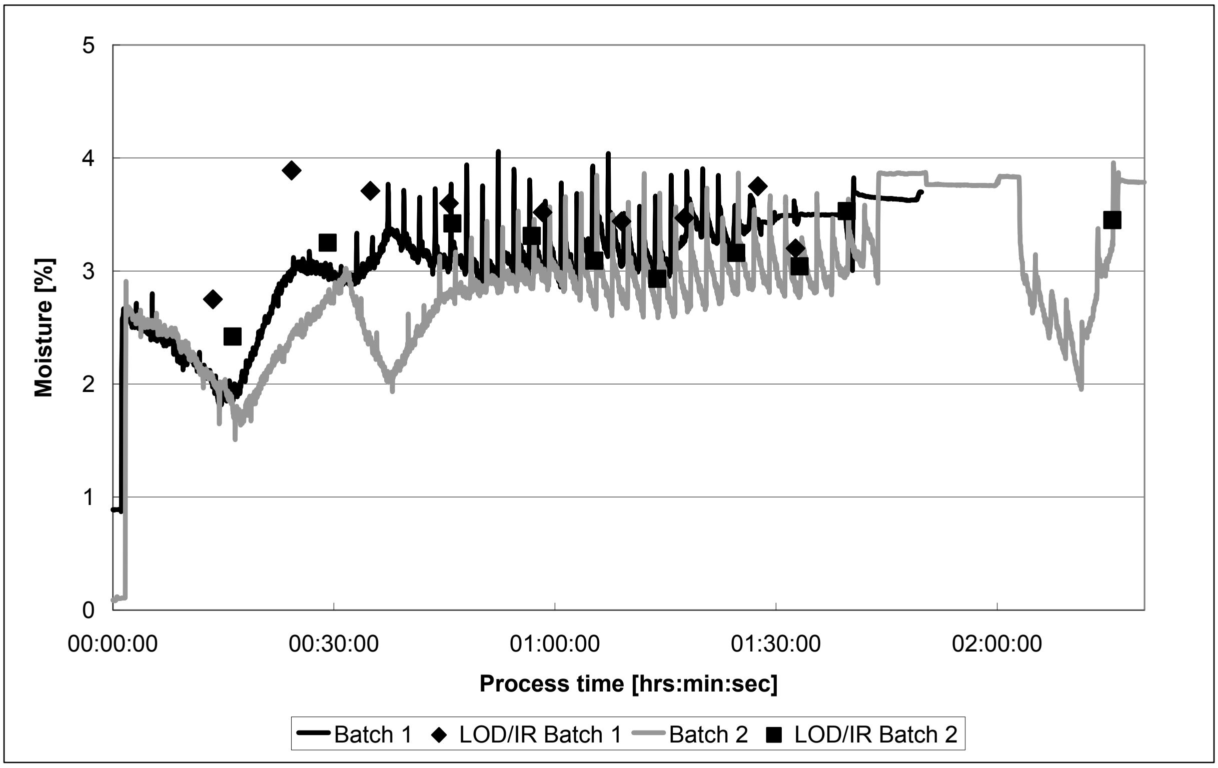

Fig. C-36: *Moisture [%] of two batches of product I recorded in-line by MRT and off-line by LOD/IR (manufacturing device: WSG 60).*

The moisture tracks of two batches of product I recorded in-line by MRT are displayed in Figure C-36.

Batch 1 consists of one API of group II (≤ 1 %), one API of group III (≤ 1 %), API PW01 of group IV (≤ 1 %), 68 % α-Lactose monohydrate, 31 % maize starch and 0.1 % calcium-EDTA-sodium. For batch 2 the composition was almost identical, except the APIs of group II and III were not included. In both cases 25 kg of a heated suspension of 5 % (m/m) maize starch were used as a binder. With the exception of two differences both curve progressions were very similar. The moisture of the second granule batch decreased by about 1 % at a process time of approximately 30 minutes, caused by an increase in product temperature.

Due to an extended analysis time of the reference method on one sample, the process of the second batch was interrupted for a couple of minutes at the end of the process. The intermittent fluidisation of the product, in combination with an incomplete covering of the sensor surface led to a constant moisture signal during this time (Fig. C-36).

The moisture signals of both batches and the respective results of the reference method LOD/IR were in a good agreement.

As observed previously the density tracks of both batches were almost identical, as can be seen in Figure C-37. In comparison with the aforementioned products, the formation of the density equilibrium at the end of the granulation process was found to be at a broader range.

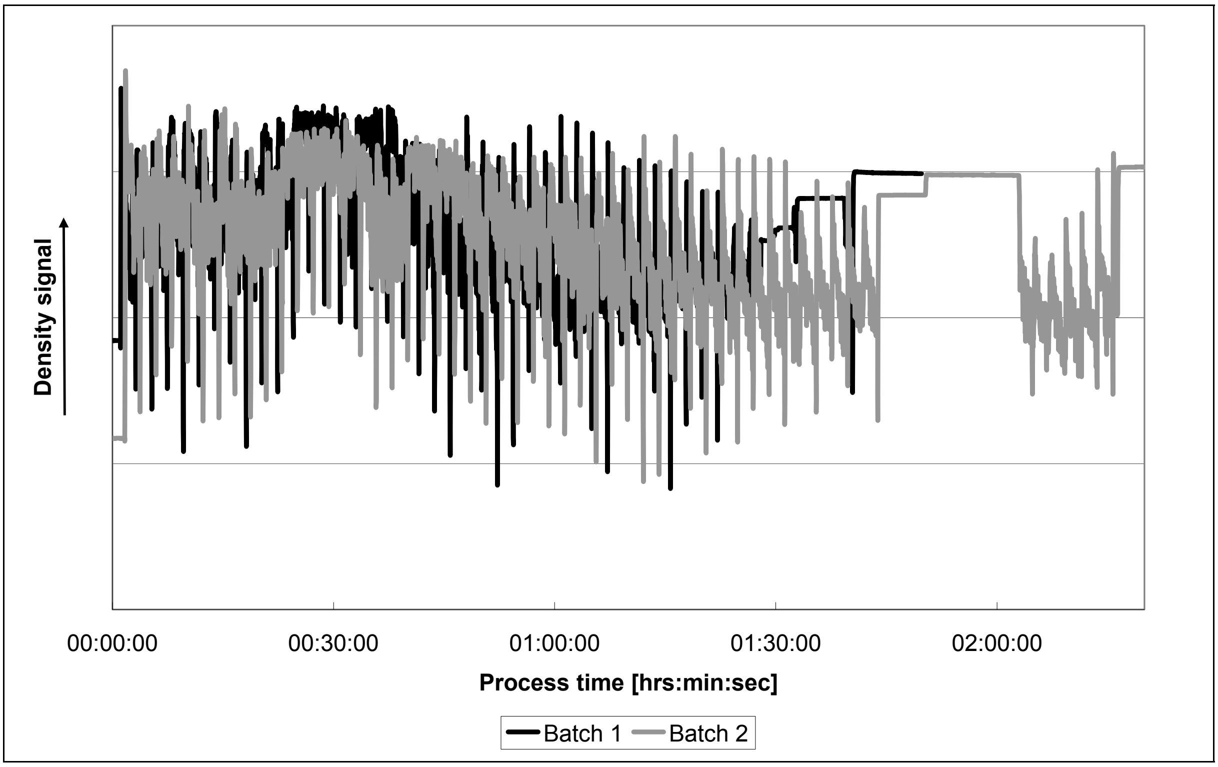

Fig. C-37: *Density tracks of two example batches of product I recorded in-line by MRT (manufacturing device: WSG 60).*

The manufacturing of this product was associated with two special features: this formulation contained a coloured API and the composition was slightly modified for the second batch. Up to now these potentially interfering factors occurred only in isolation By monitoring this product using the MRT sensor system, no negative influences on the measurement due to the combination of both factors were identified.

6.4 Conclusion

Microwave resonance technology was proven to be a valuable tool for moisture monitoring of crystal-water-containing granules with various formulations. Although the sensor system was used in the base setting without product specific calibrations, good agreements between MRT moisture measurement and the results of the reference methods were obtained for all investigated products.

The monitoring of a measuring signal correlating with product density using the MRT sensor system was found to be a useful tool to get a deeper insight into the granulation process. Particularly for the determination of the process endpoint, helpful and reliable information can be obtained due to the in-line monitoring of the density track.

For in-line moisture monitoring as well as density measurement by MRT, reproducible results were obtained for all products.

Furthermore, the microwave resonance sensor system proved to be a valuable tool for the identification of a deviating process course caused by a system failure. By performing the in-line measurement of granule moisture throughout the entire granulation process, intervention in a faulty process was possible at an early stage.

7 Impact of a differing moisture track on tabletting behaviour

7.1 Tabletting

In chapter 6 the results of the in-line moisture and density monitoring of various products were discussed. Differing moisture tracks were observed for one batch of product D and F. To investigate the impact of these deviating moisture courses on tabletting behaviour, characteristic tablet parameters, such as e.g. hardness, friability, and height were evaluated throughout the compression processes.

Using the rotary press Fette P 3000 (see chapter F 2.1.3), the granule batches of both products were compressed. At predefined time points samples were withdrawn and analyzed concerning predefined characteristics. The fixed time point for sampling and the test procedures are described in chapter F 2.

For product D, a deviating moisture course of the second granule batch was observed using the MRT sensor system. After a process time of approximately 28 minutes a moisture decrease of almost 0.8 % was recorded (see Figure C-24). If this differing moisture track has an impact on tabletting behaviour, it would be expected that the regularly performed in-process controls reveal differing compression behaviour of the second granule batch. Table C-3 provides a summary of the performed tests and the obtained results.

Table C-3: *Summary of the performed tests and the respective results obtained throughout the compression processes of product D.*

Parameter	Batch 1	Batch 2	Batch 3
Hardness (n = 44)	32 – 45 N Ø = 37 N	31 – 47 N Ø = 36 N	30 – 41 N Ø = 36 N
Height (n = 44)	2.5 – 2.6 mm Ø = 2.6 mm	2.6 – 2.6 mm Ø = 2.6 mm	2.5 – 2.6 mm Ø = 2.6 mm
Individual weight (n = 66)	79.8 – 81.9 mg Ø = 80.6 mg	79.7 – 81.4 mg Ø = 80.6 mg	80.0 – 81.1 mg Ø = 80.53 mg
Friability (n = 6.5 g)	0.06 %	0.08 %	0.11 %
	0.05 %	0.09 %	0.08 %

Table C-3: *Summary of the performed tests and the respective results obtained throughout the compression processes of product D. (continuation)*

Parameter	Batch 1	Batch 2	Batch 3
Disintegration time (n = 6)	00:00:57 – 00:01:41 Ø = 00:01:14	00:01:12 – 00:01:35 Ø = 00:01:16	00:01:06 – 00:01:31 Ø = 00:01:17
	00:01:00 – 00:01:23 Ø = 00:01:14	00:00:55 – 00:01:35 Ø = 00:01:12	00:01:03 – 00:01:24 Ø = 00:01:10
Uniformity of mass (n = 60)	77.80 – 85.00 mg Ø = 79.97 mg	78.20 – 83.00 mg Ø = 80.26 mg	78.50 – 82.60 mg Ø = 80.27 mg
	77.10 – 83.90 mg Ø = 80.13 mg	77.60 – 82.20 mg Ø = 79.84 mg	78.60 – 83.90 mg Ø = 81.02 mg
	78.30 – 85.70 mg Ø = 80.27 mg	77.90 – 85.70 mg Ø = 80.96 mg	78.80 – 84.30 mg Ø = 80.90 mg
	78.50 – 85.70 mg Ø = 80.43 mg	77.70 – 82.90 mg Ø = 79.94 mg	77.80 – 85.60 mg Ø = 80.21 mg
	78.30 – 84.70 mg Ø = 81.00 mg	78.70 – 85.30 mg Ø = 80.79 mg	78.40 – 85.00 mg Ø = 80.77 mg
	78.00 – 86.50 mg Ø = 81.10 mg	78.40 – 82.30 mg Ø = 79.92 mg	77.70 – 86.60 mg Ø = 80.92 mg

Regular testing of the tablet characteristics of the aforementioned product showed comparable results for all three batches. In all cases the results of the second granule batch were equal to the results of batch 1 and 3. An impact of the short moisture collapse of the second granule batch was not found.

While for product D the moisture course was found to be deviating for only a few minutes, for product F a differing moisture course of one batch was observed throughout the entire wet granulation process (see chapter C 6). As to be seen in Figure C-30, the moisture level of the third granule batch was about 0.8 % higher than the other two batches. To further investigate the influence of a higher moisture track throughout the entire granulation process on tabletting behaviour, tests were performed as described above.
The results of the in process controls of product F are summarized in Table C-4.

Table C-4: *Summary of the performed tests and the respective results obtained throughout the compression processes of product F.*

Parameter	Batch 1	Batch 2	Batch 3
Hardness	40 – 60 N Ø = 48 N	54 – 79 N Ø = 68 N	43 – 62 N Ø = 52 N
Height	3.1 – 3.3 mm Ø = 3.2 mm	3.0 – 3.2 mm Ø = 3.1 mm	3.1 – 3.2 mm Ø = 3.1 mm

Table C-4: *Summary of the performed tests and the respective results obtained throughout the compression processes of product F (continuation).*

Parameter	Batch 1	Batch 2	Batch 3
Individual weight	99.5 – 102.0 mg Ø = 100.6 mg	99.8 – 102.4 mg Ø = 100.8 mg	99.1 – 102.0 mg 100.6 mg
Friability (n = 6.5 g)	0.06 %	0.08 %	0.08 %
			0.05 %
	0.0 %	0.11 %	0.03 %
			0.0 %
Disintegration time (n = 6)	00:00:45 – 00:01:27 Ø = 00:01:01	00:02:06 – 00:02:38 Ø = 00:02:27	00:01:41 – 00:02:26 Ø = 00:01:57
			00:01:26 – 00:02:39 Ø = 00:01:52
	00:01:44 – 00:02:42 Ø = 00:02:14	00:01:41 – 00:02:59 Ø = 00:02:13	00:01:41 – 00:02:44 Ø = 00:02:01
			00:01:48 – 00:03:50 Ø = 00:02:34
Uniformity of mass (n = 60)	96.40 – 105.90 mg Ø = 99.33 mg	100.40 – 104.40 mg Ø = 102.11 mg	94.20 – 103.8 mg Ø = 97.44 mg
		98.20 – 103.50 mg Ø = 100.26 mg	98.70 – 110.20 mg Ø = 101.88 mg
	95.80 – 102.30 mg Ø = 98.80 mg	96.20 – 105.20 mg Ø = 100.61 mg	96.30 – 104.5 mg Ø = 99.97 mg
		99.50 – 105.90 mg Ø = 101.48 mg	95.90 – 110.00 mg Ø = 100.30 mg
	95.00 – 107.10 mg Ø = 99.96 mg	95.70 – 101.50 mg Ø = 98.71 mg	98.10 – 107.00 mg Ø = 102.42 mg
		98.50 – 104.40 Ø = 100.68 mg	96.30 – 107.80 mg Ø = 100.14 mg
	97.60 – 105.40 mg Ø = 100.40 mg		97.30 – 106.70 mg Ø = 100.60 mg
			95.10 – 106.70 mg Ø = 100.08 mg

For all performed tests, tablet characteristics of the third batch were comparable to the other batches. The disintegration times of the three batches were found to differ slightly. However, the results of the third batch were found to be between batch one and two. It was not possible to associate this result with the observation of a differing moisture track of the third batch.

7.2 Conclusion

As all formulations have been thoroughly validated in the company's routine practice, an impact of the process/ quality parameters, slightly varying within the validated ranges, was excluded. An influence of a differing moisture track throughout the granulation process on subsequent tablet behaviour was not detected. The investigated batches showed comparable test results. However, the measured moisture difference was very slight (± 0.8 %) in both cases. It is doubtless that stronger fluctuations in the moisture track, beyond the validated range, are associated with impacts on granule properties and therefore on tabletting behaviour. Thus, in-line moisture monitoring is a valuable tool to ensure product quality. Prior investigations showed that a reliable determination of the drying endpoint and the moisture monitoring throughout the entire process is enabled. Furthermore, the detection of faulty process courses becomes possible. Due to the in-line monitoring of granule moisture, considerable benefits for product quality and process understanding were achieved.

8 Moisture measurement by MRT at high moisture levels

Due to the moisture sensitivity of the APIs used in the previous production processes wet granulation was usually performed at moisture ranges < 7.5 %. Within this range, good correlations between the granule water content measured in-line by MRT and both reference methods, KF and LOD/IR were obtained.

However, during a drying process of wet granules under moisture monitoring by MRT increased deviations between MRT and the reference method LOD/IR were observed with increasing granule water contents (see chapter C 2 and C 4).

In order to investigate this phenomenon two experimental series were performed focussing on moisture levels > 7.5 % throughout the granulation process. For comparison against a reference method, samples were withdrawn throughout the entire process and analyzed off-line by LOD/IR. To observe the direct effect of high moisture contents on MRT moisture measurement, the sensor system was not previously calibrated.

8.1 Moisture monitoring of product C

A first wet granulation experiment was performed under test conditions in the fluidized bed granulator GPCG 15 at a considerably higher moisture level than used previously. The manufacturing process of a granule batch consisting of 33 % MCC and 67 % α-Lactose monohydrate was monitored in-line using the microwave resonance sensor system. During spraying, 20 kg of an aqueous solution of 5.5 % povidone 90 was applied as a binder. Throughout the entire process, samples were withdrawn and their water content was determined by LOD/IR.

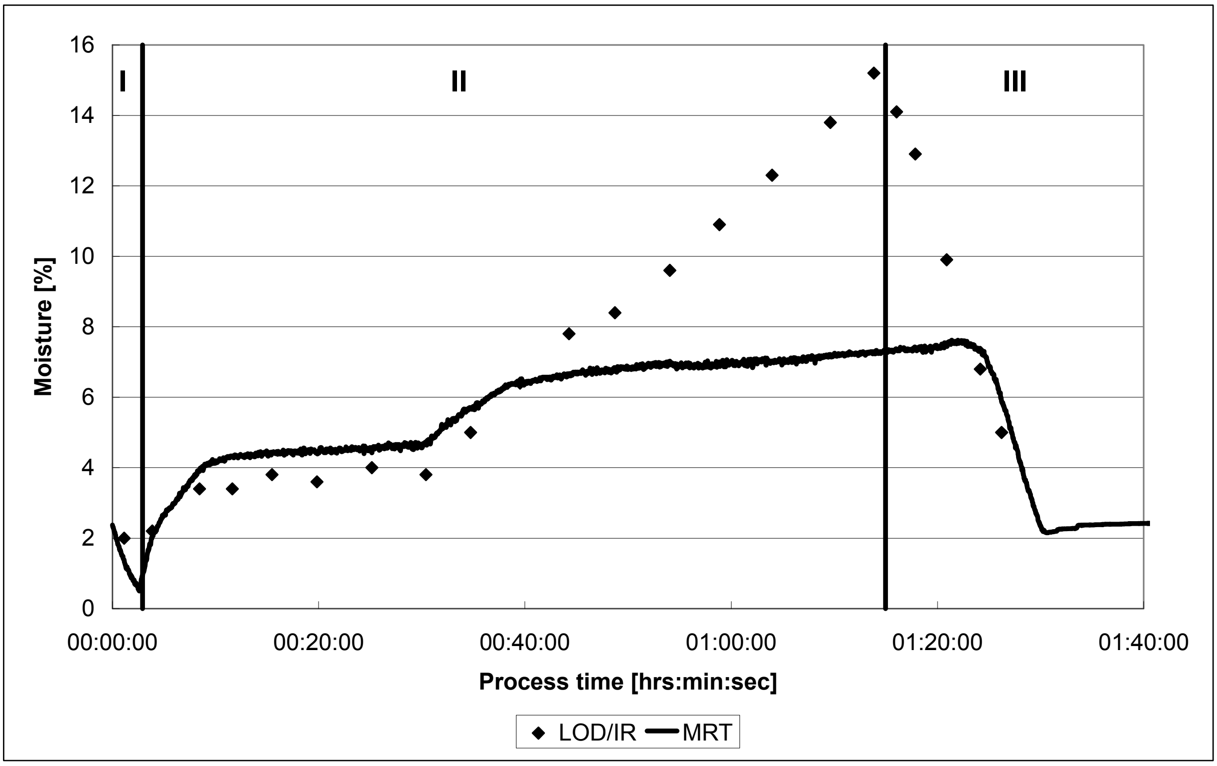

Fig. C-38: *Moisture tracks [%] of one example batch of product C recorded in-line by MRT and off-line by LOD/IR (manufacturing device: GPCG 15). I = pre-heating, II = spraying, III = drying phase*

Figure C-38 provides the moisture track recorded in-line by the MRT sensor system and the results of water determination obtained by LOD/IR.

While the moisture content increased quickly at the beginning of the spraying phase (II), it settled down to a moisture value of approximately 4.4 % after a spraying time of 7 minutes. In this moisture range, a good agreement between the moisture recorded in-line by MRT and the reference method was observed. In order to achieve higher granule water contents, the parameter settings were adjusted. The spraying rate was enhanced from about 240 g/min up to 280 g/min while the inlet air temperature was simultaneously reduced from 60°C to 55°C after a process time of approximately 28 minutes. In the following 10 minutes a moisture increase of approximately 2 % was recorded by the MRT sensor. Afterwards the moisture increased very slowly to nearly 8 %.

By evaluating the results of the off-line moisture determination a striking phenomenon was found. While the granule moisture content recorded by the MRT sensor seemed to increase very slowly from approximately 6 % to nearly 8 %, a very fast moisture increase was determined by LOD/IR. The maximum value of the water determination by LOD/IR was found to be approximately 16 % and therefore considerably higher than the moisture recorded by MRT.

Furthermore, it was remarkable that the sensor system detected the drying of the granules only at moisture ranges < 7 %. In fact, the sensor showed a slight increase in moisture content during the first minutes of drying. Obviously a reliable moisture measurement of this product is only possible at moisture contents < 7 %.

In Figure C-39 the recorded MRT moisture values were plotted against the results of moisture determination by LOD/IR. Until a moisture content of approximately 7 % was reached, the relation was nearly linear. Above moisture contents of 7 %, an explicit threshold was observed. While LOD/IR moisture results showed a considerably increase the recorded MRT value remained nearly constant. This critical threshold was found to cause the increasing deviations between MRT and LOD/IR moisture, recorded at moisture contents > 7 % for this product.

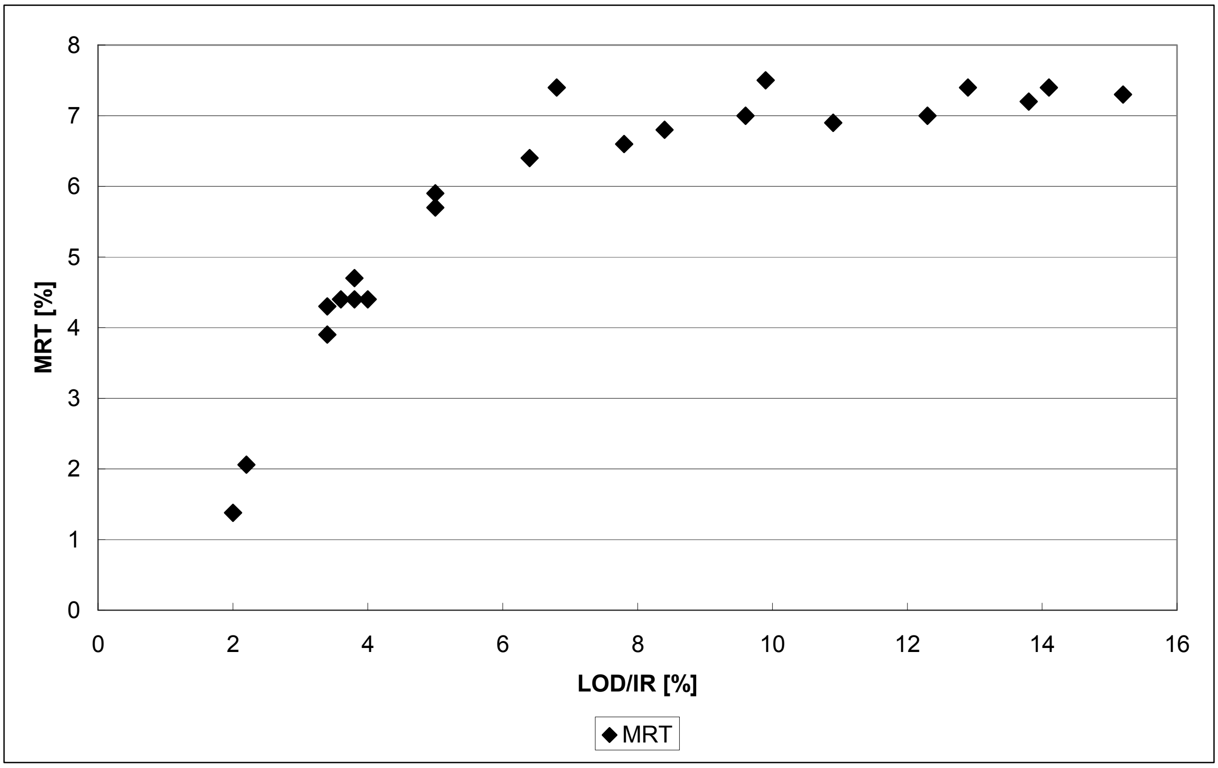

Fig. C-39: *Correlation of the recorded MRT moisture and the results of the off-line water determination by LOD/IR for one example batch of product C (manufacturing device: GPCG 15).*

8.2 Moisture monitoring of product J

In order to verify to what extent these phenomena can be observed for various formulations one further experimental series was performed. A granulation process of two granule batches consisting of 67 % α-Lactose monohydrate and 33 % maize starch were monitored in-line using the MRT sensor system. Wet granulation was performed applying 15 kg of an aqueous solution of 6 % povidone 90. The first granule batch was produced under constant conditions. The aim of this procedure was to achieve a high moisture level in a short time by applying the binder with a high spraying rate, in this case approximately 320 g/min.

To investigate the impact of the spraying rate on MRT moisture measurement, the spraying rate was adjusted stepwise during the production of a second batch. Initially the spraying rate was 100 g/min. Then it was increased step by step of about 50 g/min after every application of 2.5 kg of binder solution. The final rate was adjusted to be 350 g/min.

If the rate of binder application has a negative influence on MRT moisture measurement, an abrupt change of the MRT signals from the LOD/IR course would be expected.

In Figure C-40, the MRT values are plotted against their respective results of water determination by LOD/IR for both granule batches.

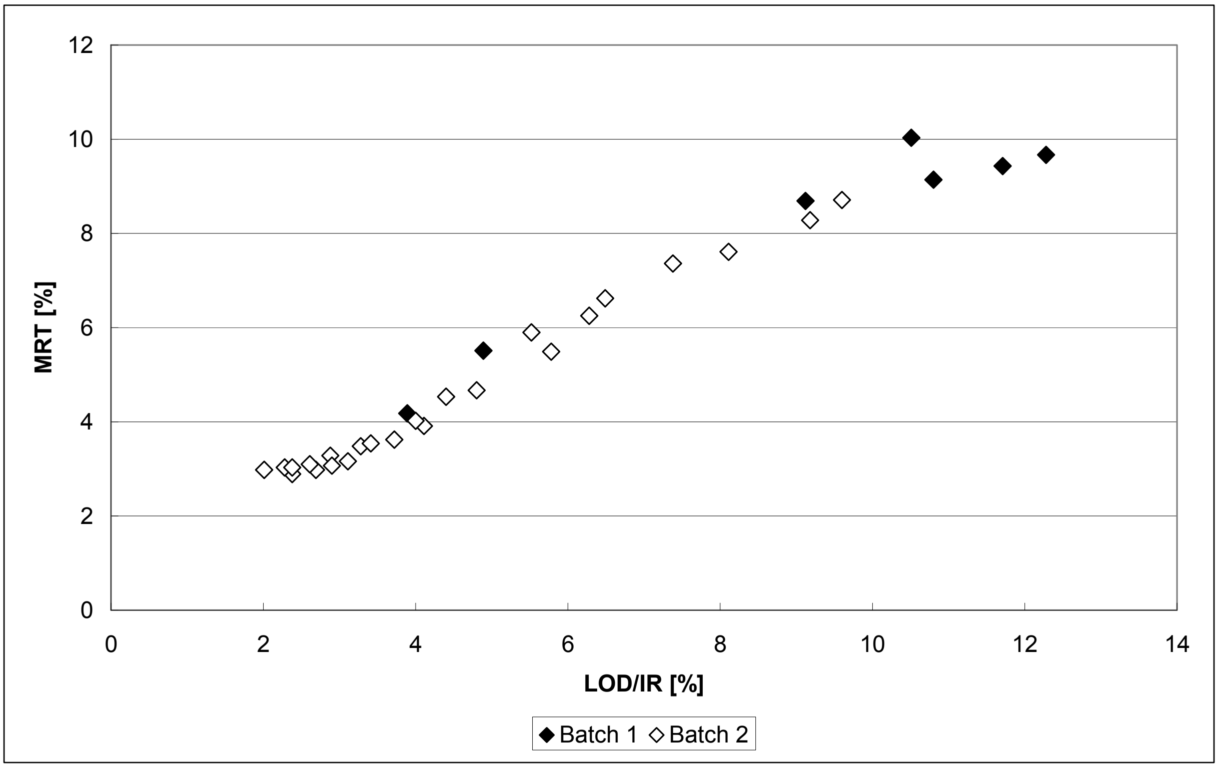

Fig. C-40: *Correlation of the recorded MRT moisture to the results of the off-line water determination by LOD/IR for two batches of product J (manufacturing device: GPCG 15).*

By applying the aqueous binder solution at a constant spraying rate of 320 g/min, a maximum granule water content of nearly 12.3 % (LOD/IR) was achieved for the first batch. For the first granule batch a slight threshold was found at a moisture range of 10 – 11 %. However, it was worth noting that this threshold was considerably less pronounced than that observed for the granule composition described previously (see chapter C 8.1).
Due to a lower spraying rate throughout the granulation process, the highest moisture content of the second granule batch was found to be approximately 9.6 %.

By plotting both the MRT moisture and the results of water determination by LOD/IR of the second granule batch against the process time, the moisture course throughout the entire granulation process becomes visible (Figure C-41). Furthermore, Figure C-41 illustrates the various phases of this wet granulation process with the typical phases preheating (I), spraying (II – VII) and drying (VIII). In this case the spraying phase is subdivided due to the varying application rate of the binder solution.

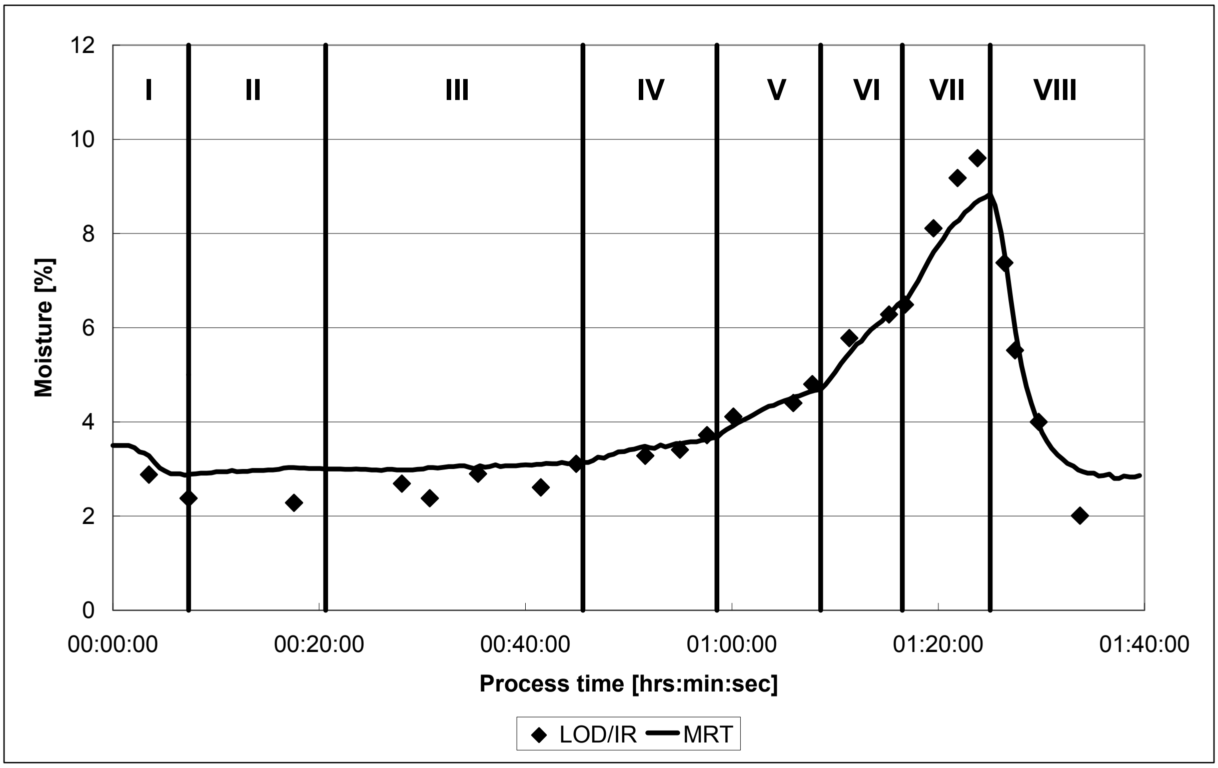

Fig. C-41: *MRT values [%] and results of the water determination by LOD/IR [%] of batch 2 of product J throughout the entire wet granulation process (manufacturing device: GPCG 15). I = preheating, II = spraying rate: 100 g/min, III = 150 g/min, IV = 200 g/min, V = 250 g/min, VI = 300 g/min, VII = 350 g/min, VIII = drying*

The previously mentioned potentially negative impact of the rate of binder application would be expected to cause an abrupt increase in the deviation between MRT and the LOD/IR curves, at the time points of the increase in spraying rate. Within this investigation, such an effect on moisture determination by microwave resonance technology was not observed. In fact the curve progressions of both MRT and LOD/IR were found to be quite similar. A negative influence of the rate of spraying on the relation of moisture determination by MRT and LOD/IR was not found.

8.2.1 Granule properties

To further investigate the impact of various spraying rates, and their associated differing moisture courses on granule properties, characteristic granule parameters were determined.

Particle size distribution of granules

The particle size distributions of both granule batches of product J were determined, to evaluate the effects of varying spraying rates on particle sizes. The test was performed as described under chapter F 2.3.2

Figure C-42 displays the cumulative undersize fractions [%] determined by sieve analysis.

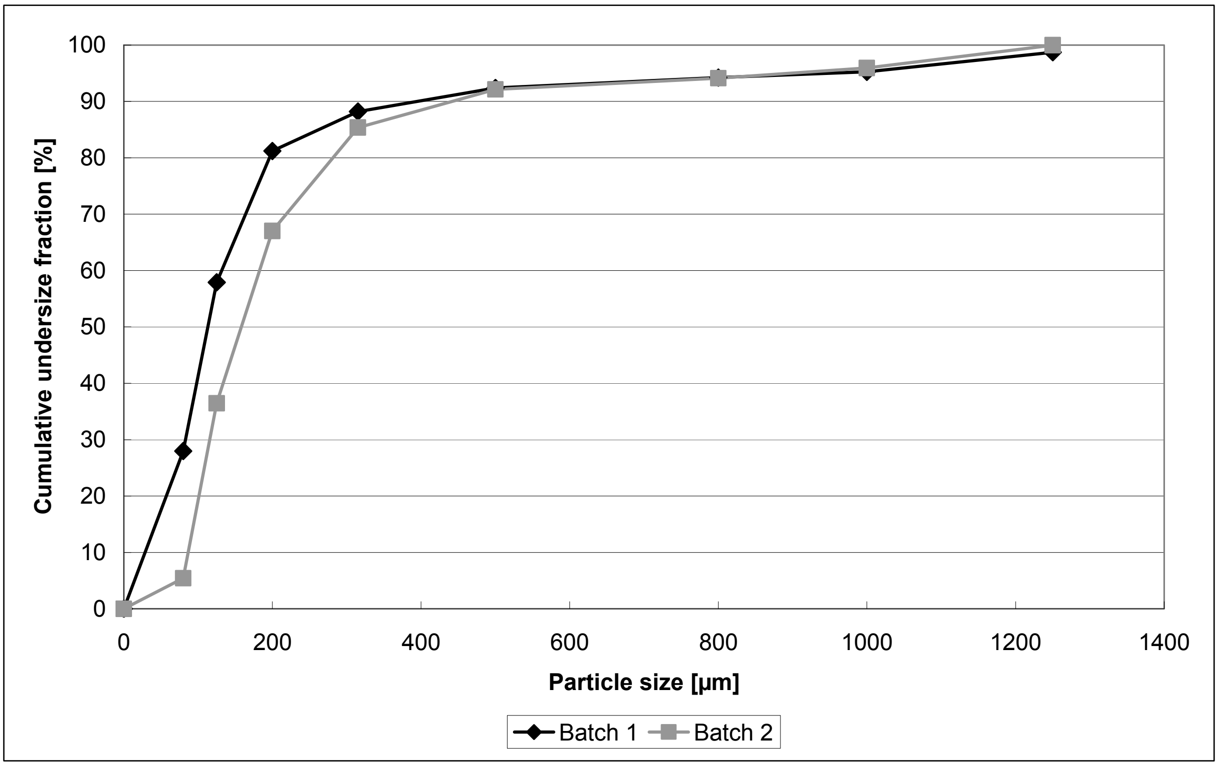

Fig. C-42: *Cumulative undersize curves of both granule batches of product J. (n = 3, mean)*

Comparing the determined cumulative undersize curves of both batches, a tendency to smaller particles was observed for the first batch. For particle sizes ≥ 500µm the curves of both batches were almost identical. The different spraying rates of both batches may be a reason for the slightly smaller particles of batch 1.

Granule flowability

Granule flowability is an important quality determining parameter, and was determined by the ring shear cell tester (see F 2.3.3). For subsequent processing, e.g. tabletting, good flow properties of the granules are required. Therefore, flowability was determined to evaluate the influence of different spraying profiles on granule flow properties.

Figure C-43 displays the results for both granule batches of product J.

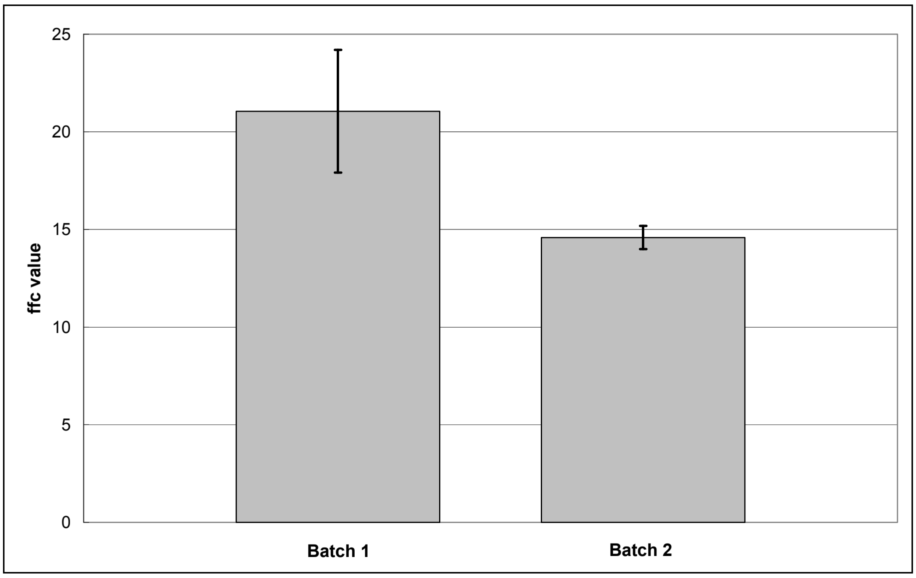

***Fig. C-43**: ff_c values of both granule batches determined by the ring shear cell tester. (n = 3, mean ± SD)*

The ratio of consolidation stress to the unconfined yield strength value, describes the flow properties of a bulk substance and is defined as ff_c value (flow function). Flowability improves with increasing ff_c value. Depending on the ratio of consolidation stress and unconfined yield strength, flow behaviour ranges from non-flowing ($ff_c < 1$), very cohesive ($1 < ff_c < 2$), cohesive ($2 < ff_c < 4$), easy-flowing ($4 < ff_c < 10$) to free-flowing ($ff_c > 10$) characteristics.

For both granule batches, very high ff_c values were found (batch 1: 21.05, batch 2: 14.59). Both batches showed free-flowing characteristics by considerably exceeding the ff_c value of 10. For the first granule batch, produced with a constant high spraying rate, a higher value was found than for the second batch. As both batches showed very high ff_c values, a measurable influence of this difference on further processing is not expected.

Scanning electron microscopy

To visualize granule surfaces, scanning electron microscopy (SEM) was used. Micrographs were made as described under chapter F 2.3.4 at magnifications of 150x and 500x. Example micrographs of both granule batches are to be seen in Figure C-44.

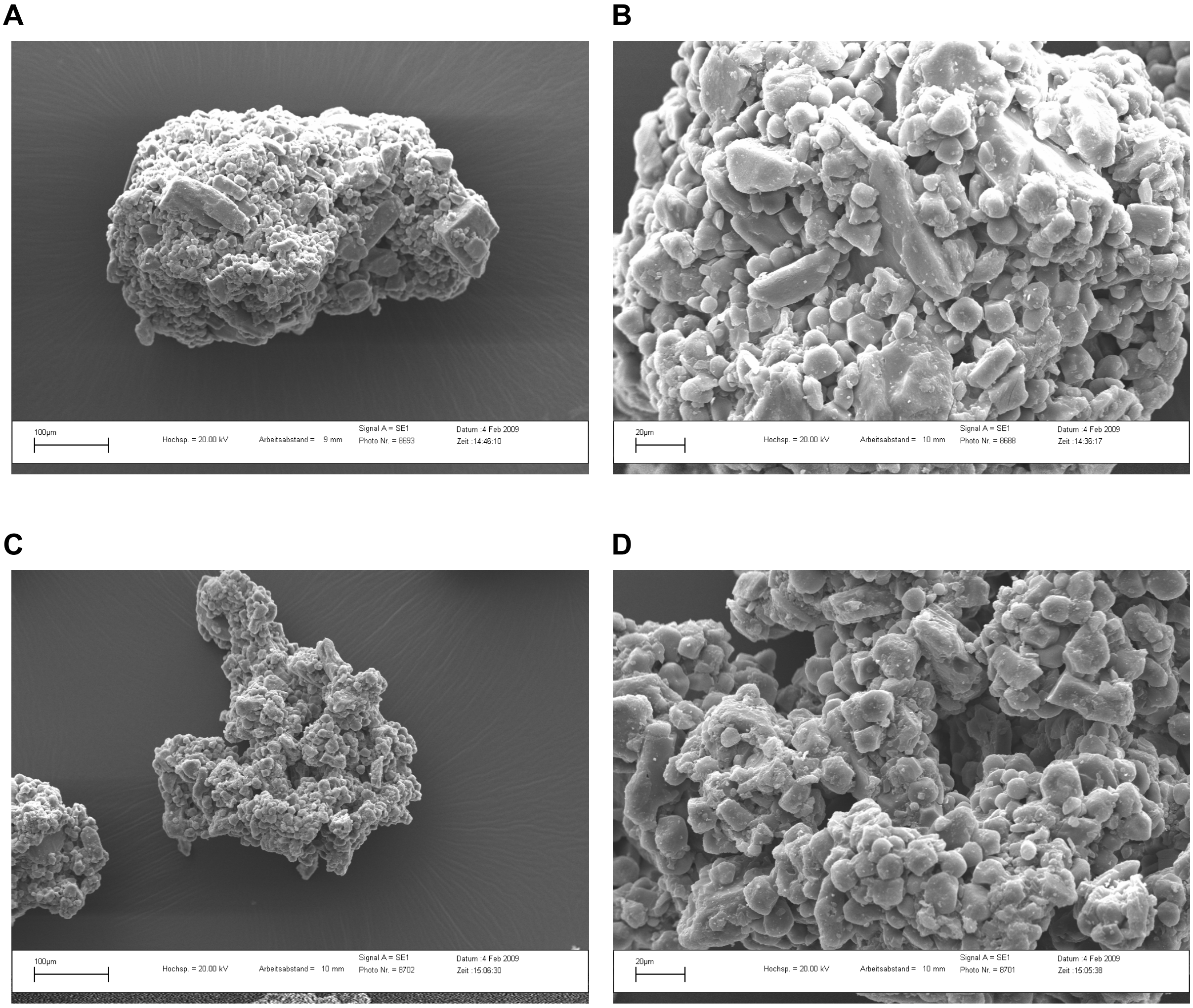

Fig C-44: *Micrographs of granule batches of product J produced with different spraying rates. A) batch 1: constant spraying rate, scale: 100µm, adjusted magnification 150x, B) batch 1: constant spraying rate, scale: 20 µm, adjusted magnification 500x, C) batch 2: varying spraying rate, scale: 100 µm, adjusted magnification 150x, D) batch 2: varying spraying rate, scale: 20µm, adjusted magnification 500x*

For the second batch, produced with varying spraying rates, a more varying granule structure and surface is seen than for the first batch (Figure C-44 A, C). At a magnification of 500x small holes are apparent in the structure of the second batch (Figure C-44 D). In both cases, individual particles of the contained substances could still be identified on granule surfaces.

8.3 Conclusion

The increasing deviations between MRT moisture and the results of the reference methods, observed in production processes with high moisture contents, were verified in both performed experimental series.

For product C, a remarkable moisture track was observed. Up to a moisture content of approximately 7 % both MRT and LOD/IR correlated well. Above this identified threshold, MRT signals stayed nearly constant while LOD/IR results increased considerably. Obviously an evaluation of the MRT signals above the threshold was not possible.

For the second investigated granule composition (product J), a comparatively weak threshold was found at a moisture content of 10-11 %. In this case the impact on moisture monitoring by MRT was only marginal. An influence of the spraying rate on this effect was not identified. Also an impact of this slightly differing moisture course (about 0.8 % difference) on tabletting behaviour was not identified.

In summary, the existence of a threshold was demonstrated to be the reason for the increasing deviations between MRT moisture measurement and the reference methods at higher granule water contents. The localization of the threshold and the dimension of its impact on MRT moisture measurement were found to depend directly on granule composition, but hardly predictable up until now.

Within this study the final cause for the existence of a threshold could not be entirely clarified. Depending on the main aim of using the MRT sensor system, different demands on the sensor have to be made. For the identification of the drying endpoint at low water contents, the existence of the threshold at higher moisture values could be neglected. In contrast the monitoring of the moisture track throughout the entire wet granulation process at high moisture contents is expected to be influenced by the threshold. The identification of the location of the threshold is a precondition for the evaluation of the recorded results. As it seems to depend on the product composition, thorough calibration procedures are recommended. The revision of the evaluating software may offer a solution for this measuring problem in the future.

9 Impact of particular substances on moisture monitoring by MRT and final granule quality

Within previous studies, another interesting phenomenon was observed: in some products the MRT moisture was found to be less than both reference methods, KF and LOD/IR. Actually MRT moisture exceeded the off-line results slightly (see chapter C 6). Substances with swelling character contained in the formulations, were assumed to cause this phenomenon. Due to their swelling properties, they could embed water molecules into the swollen structure resulting in a constricted mobility of the water molecules. Consequently, not all water molecules are detectable by MRT.

In order to verify this approach, two experimental series were performed. In both cases a substance with swelling properties, either PPMS or crospovidone, was contained in the composition. Multiple granule batches with an increasing proportion of the respective substance were produced under comparable process conditions. Simultaneously, samples were withdrawn throughout the entire process in order to determine their water content off-line by LOD/IR. To observe the direct effect of these excipients on MRT moisture measurement, the sensor system was not calibrated beforehand.

9.1 Crospovidone

Crospovidone (crosslinked polyvinyl-pyrrolidone, registered trade name: Kollidon® CL) is an insoluble polyvinyl-pyrrolidone with the form of a “popcorn” polymer [Quadir 2006]. Due to its property to swell very quickly the main function of crospovidone (CL PVP) is to be a super-disintegrant. CL PVP has been reported to be able to absorb more than 50 % of its own mass in water [Shangraw 1981]. Based on this attribute, CL PVP was chosen as the first test substance for the investigation of the influence of swelling agents on MRT moisture measurement.

9.1.1 Moisture measurement

In the first experimental series granule batches of product K consisting of α-Lactose monohydrate and increasing parts of CL PVP (2.5, 5, 10 and 20 %) were produced in the fluidized bed granulator GPCG 15. A 6 % (m/m) aqueous solution of povidone 30 was applied as a binder.

Table C-5 provides a summary of the composition of the produced test batches. With regard to the aforementioned hypothesis, it was expected that differences between MRT moisture and the results of the reference method LOD/IR increase with increasing parts of crospovidone.

***Table C-5**: Percentage composition of test batches of product K.*

Batch	Crospovidone	α-Lactose monohydrate	Granulating fluid
1	2.5 % (m/m)	97.5 % (m/m)	6 % aqueous solution of povidone 30
2	5 % (m/m)	95 % (m/m)	
3	10 % (m/m)	90 % (m/m)	
4	20 % (m/m)	80 % (m/m)	

Throughout the entire granulation process, samples were withdrawn and analyzed off-line by LOD/IR. Subsequently the residues of MRT - LOD/IR were calculated and plotted against the results of moisture determination by LOD/IR.

With increasing amounts of CL PVP, a strong tendency to negative values of the calculated residues to negative values was observed (see Figure C-45).

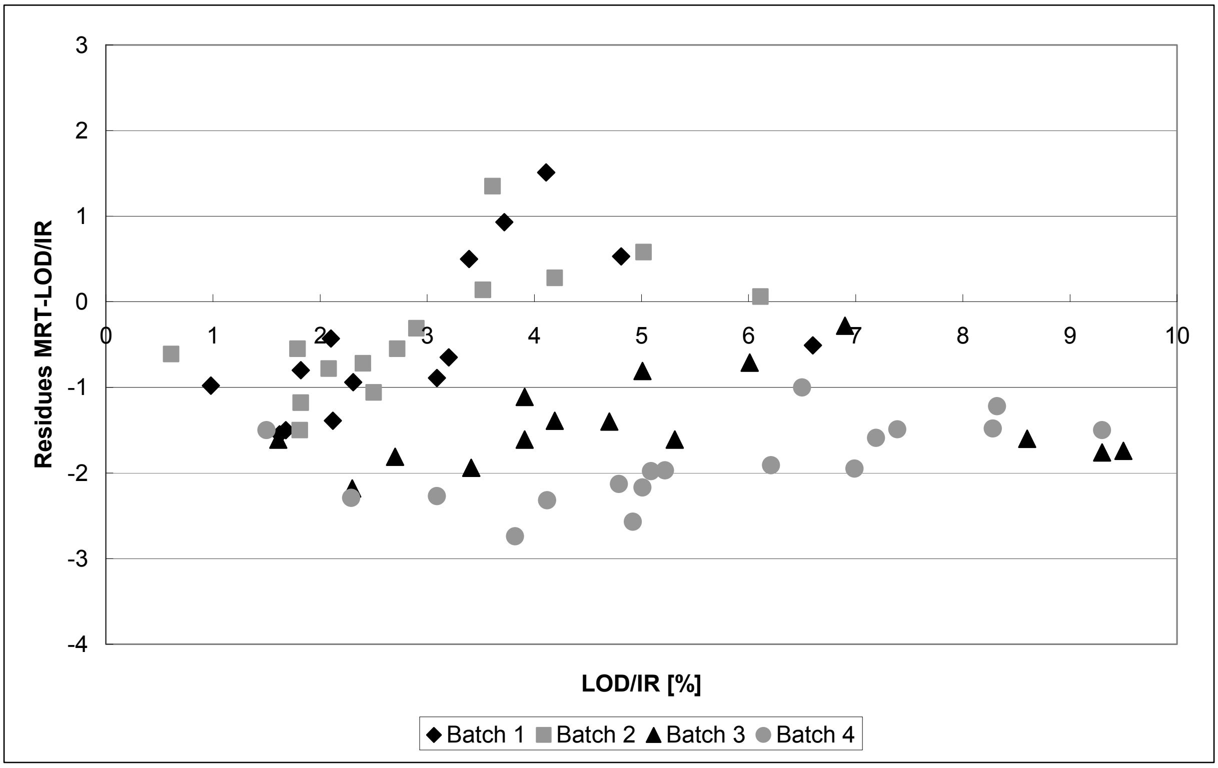

Fig. C-45: *Residues of MRT moisture [%] produced with increasing amounts of crospovidone plotted against moisture [%] results determined by LOD/IR (manufacturing device: GPCG 15).*

The behaviour of batch 1 (2.5 % CL PVP) and batch 2 (5 % CL PVP) appeared to be quite similar. Up to moisture value of approximately 3 %, residues were found to be negative, with a typical range of – 0.5 to -1 %. Within the moisture range of 3 % to 6 %, the residues were found to be positive for batch 1 and 2. Considering the complete moisture range of both batches, a clear tendency to a specific range was not identified. In fact the residues were balanced between positive and negative values throughout the entire process.

In contrast, the third (10 % CL PVP) and fourth (20 % CL PVP) batches showed only negative residues throughout the entire moisture range. It was observed that the fourth batch with the highest amount of CL PVP showed the highest negative residues throughout the process (-1 to -3%). Furthermore, it was observed that with increasing amounts of CL PVP, the residues tended more and more to negative values.

Depending on the fraction of CL PVP, an increasing deviation between MRT moisture measurement and the reference method was found. This observation confirms the thesis that swelling agents prevent water molecules from being determined by MRT.

Furthermore, significantly higher moisture values during the granulation process were recorded with increasing amount of CL PVP (see Figure C-45). While the first granule batch reached its highest water content at approximately 6 %, the maximum moisture of the fourth batch, which contained eight times the amount of the swelling agent, was found to be nearly 9.5 %.

The increasing amount of CL PVP resulted not only in increasing deviations between both applied methods for moisture determination, but also into a higher absorption of water by the solid particles. This observation fits with the aforementioned data in the literature, whereby CL PVP is able to absorb more than 50 % of its own mass in water from the environment.

Due to the high impact of this swelling agent on MRT moisture measurement, it can be concluded that a calibration of the sensor signal is required for each ratio of CL PVP and other contained substances. A classification to a superordinated calibration group is not recommended.

9.1.2 Granule properties

To evaluate the influence of the varying amount of crospovidone on granule properties, various measurements were performed.

Particle size distribution of granules

The particle size distributions of the granule batches produced with varying amounts of crospovidone were determined by sieve analysis (F 2.3.2).

As seen in Figure C-46, the cumulative undersize curves of batches 1, 2 and 4 were nearly identical. The cumulative undersize fractions for a particle size up to 200 µm were found to be nearly 90 % for the three batches. In contrast, the third batch showed a considerable lower value (nearly 36 %) for particle sizes up to 200 µm.

Also the following curve progression of the third batch deviates from the curves of batches 1, 2 and 4. The cumulative undersize fraction of the third batch was found to run below the curves throughout the measured range. As all batches were produced under comparable process conditions, parameter settings were excluded as the reason for the differing particle size distribution.

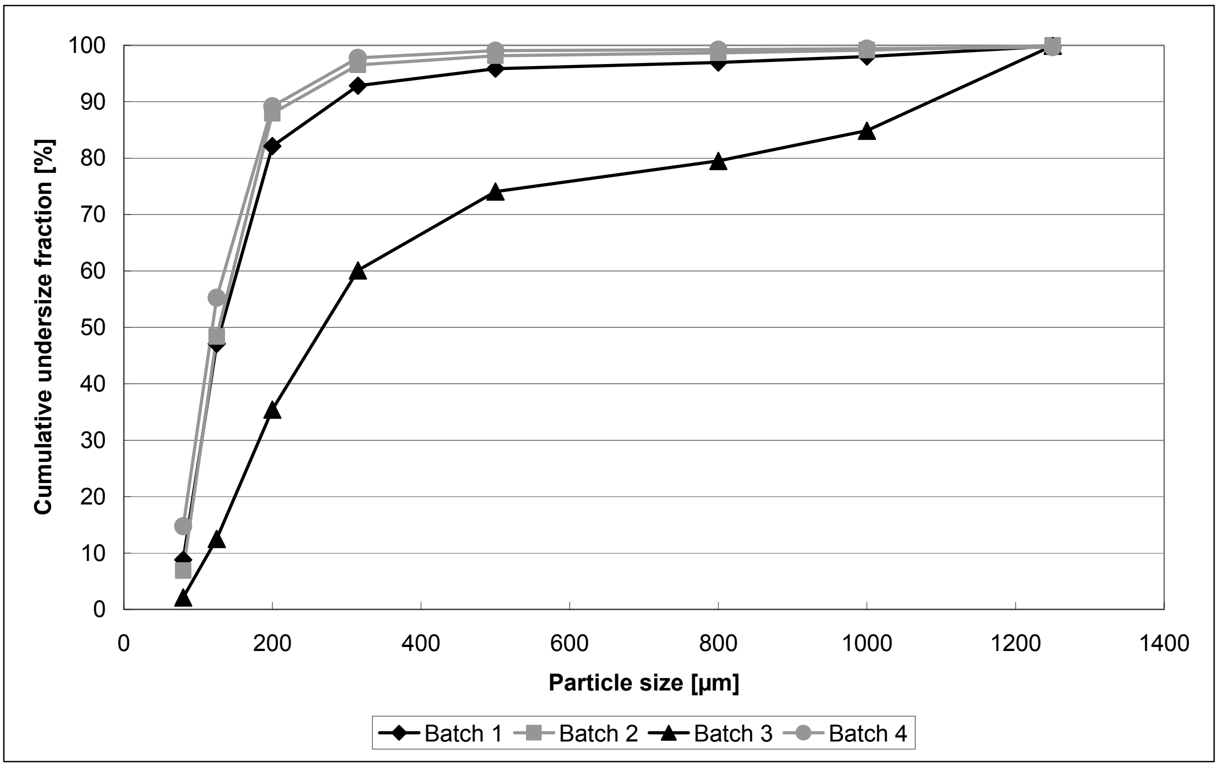

***Fig. C-46:** Cumulative undersize curves of granules produced with varying amounts of crospovidone. (n =3, mean)*

Granule flowability

Granule flowabilities of the four batches were determined by a ring shear cell tester (see chapter F 2.3.3). The results are displayed in Figure C-47.

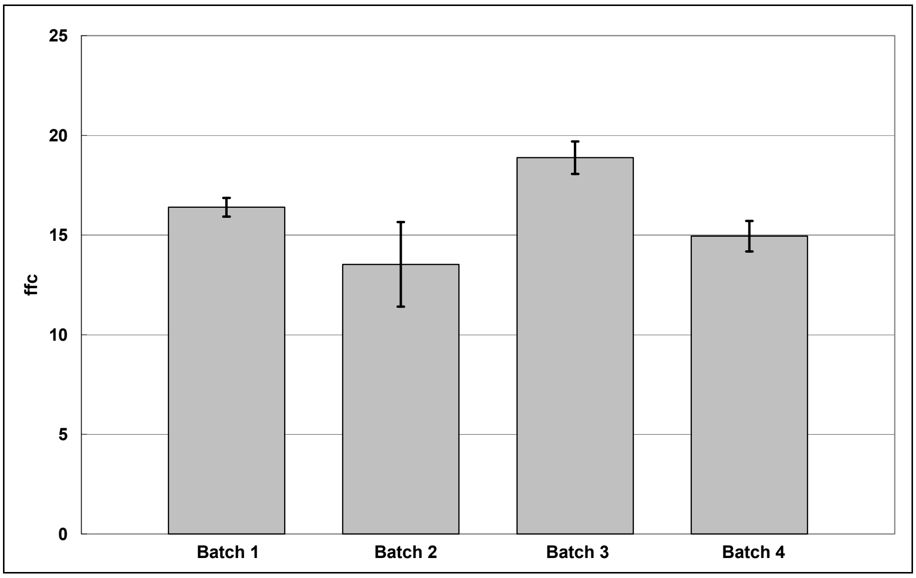

Fig. C-47: *Granule flowability of batches produced with varying amounts of crospovidone. (n = 3, mean ± SD)*

For all batches the measured ff_c values were considerably higher than 10. Results independent of the amount of CL PVP were obtained. Although the third batch (10 % CL PVP) showed a differing particle size distribution all four batches showed free-flowing properties.

Scanning electron microscopy

For the visualization of granule surfaces scanning electron microscopy was used with magnifications of 150x and 500x (chapter F 2.3.4).

In Figure C-48 example micrographs of batch 1 (A, B, 2.5 % CL PVP) and batch 2 (C, D, 5 % CL PVP) are displayed.

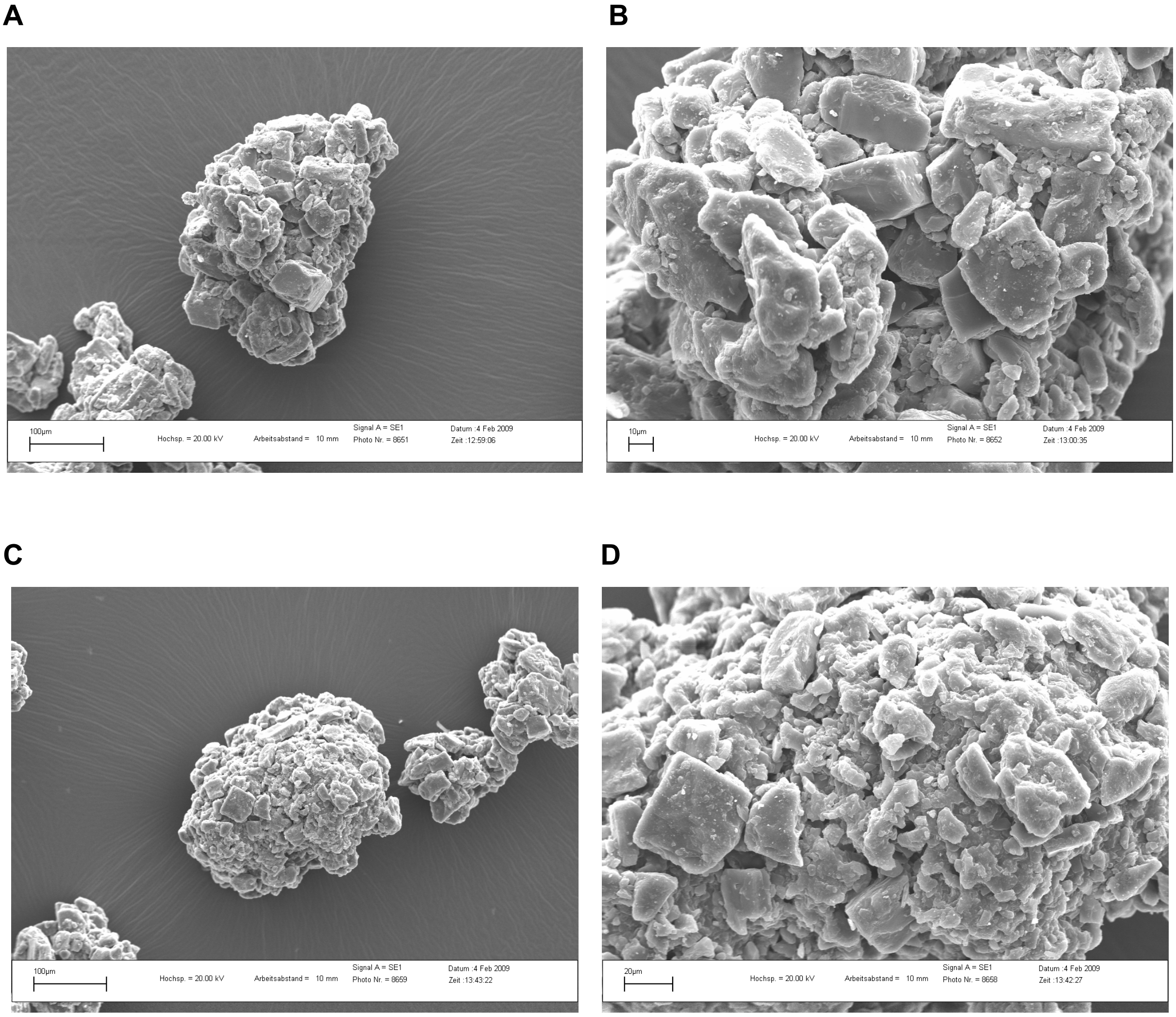

Fig. C-48: *Scanning electron micrographs of the test batches with varying amount of CL PVP. A) 2.5 % CL PVP, scale: 100 µm, adjusted magnification: 150x, B) 2.5 % CL PVP, scale: 10 µm, adjusted magnification: 500x, C) 5 % CL PVP, scale: 100 µm, adjusted magnification: 150x, D) 5 % CL PVP, scale: 20 µm, adjusted magnification: 500x*

Figure C-49 shows scanning electron micrographs of the test batches with high amounts of CL PVP.

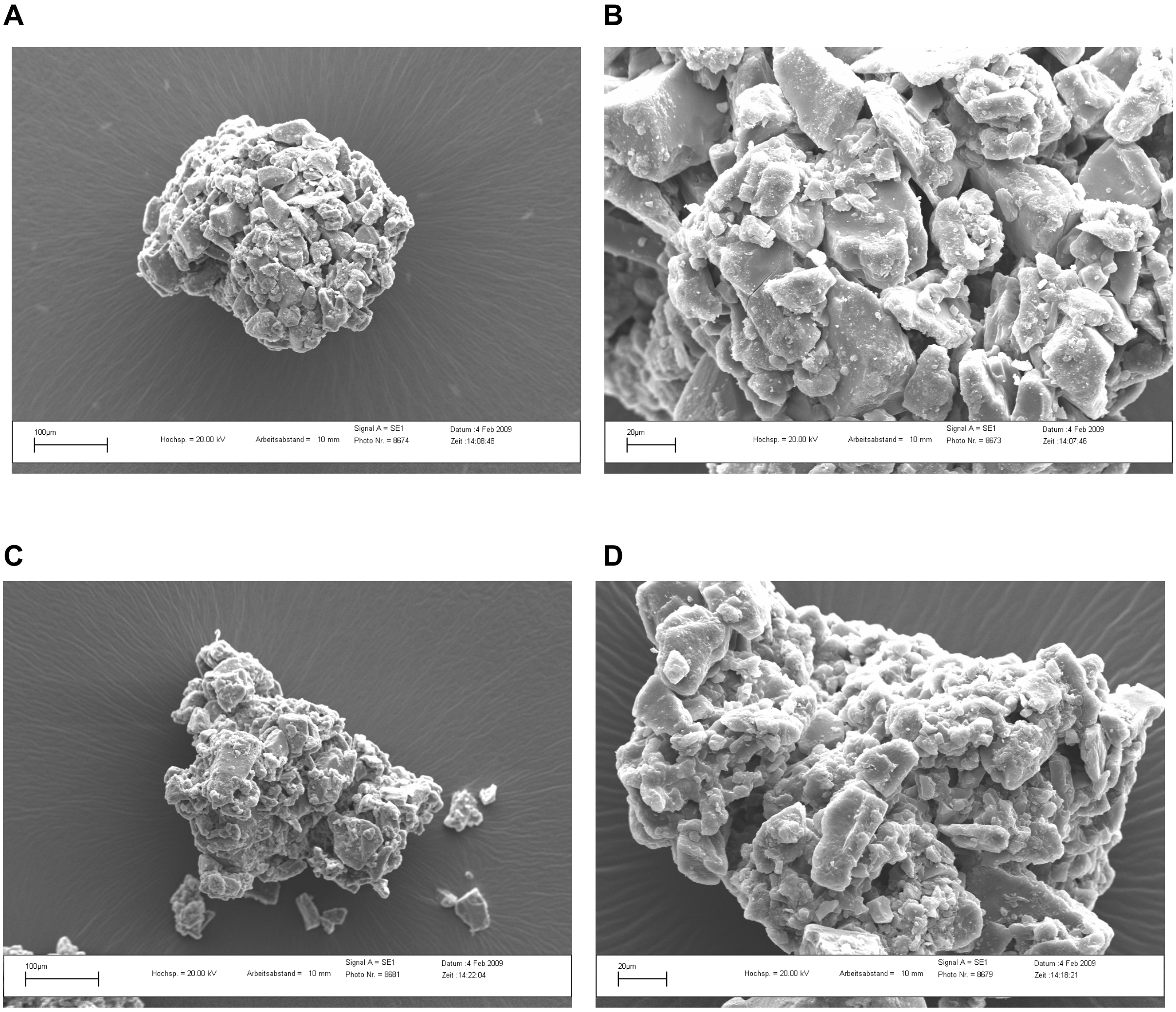

Fig. C-49: *Scanning electron micrographs of the test batches with varying amount of CL PVP. A) 10 % CL PVP, scale: 100 µm, adjusted magnification: 150x, B) 10 % CL PVP, scale: 20 µm, adjusted magnification: 500x, C) 20 % CL PVP, scale: 100 µm, adjusted magnification: 150x, D) 20 % CL PVP, scale: 20 µm, adjusted magnification: 500x*

Differences between granule surfaces were not apparent. Independent of the proportion of CL PVP, surfaces of all four batches were irregular with porous character. Individual particles of α-Lactose monohydrate could be identified on all granule surfaces.

9.2 Partially pregelatinized maize starch

Due to its partially solubility in cold water, partially pregelatinized maize starch (PPMS, tradename: Starch 1500®) is used during wet granulation processes as a binding agent as well as disintegrant.

In a previous study, it was observed that MRT measured lower water contents than LOD/IR for granules containing PPMS (see chapter C 6.1). Therefore, PPMS was chosen as a second model excipient for the investigation of the impact of swelling agents on MRT moisture measurement.

9.2.1 Moisture measurement

Under experimental conditions, granule batches containing α-Lactose monohydrate as the main fraction were produced in the fluidized bed granulator GPCG 15. The different amounts of PPMS used are summarized in Table C-6.

***Table C-6**: Percentage composition of test batches of product L.*

Batch	**Partially pregelatinized maize starch (starch 1500)**	**α-Lactose monohydrate**	**Granulating fluid**
1	20 % (m/m)	80 % (m/m)	6 % aqueous solution of povidone 30
2	30 % (m/m)	70 % (m/m)	
3	40 % (m/m)	60 % (m/m)	

The evaluation of the impact of PPMS on moisture measurement by MRT was performed in the same manner as described for crospovidone (see chapter C 9.1).

For comparison of the recorded MRT moisture to a reference method, samples were withdrawn throughout the process and analyzed off-line by LOD/IR. Afterwards the residues were calculated.

By plotting the calculated residues against LOD/IR, a similar behaviour of all produced batches was observed independent of the contained fraction of PPMS (Figure C-50).

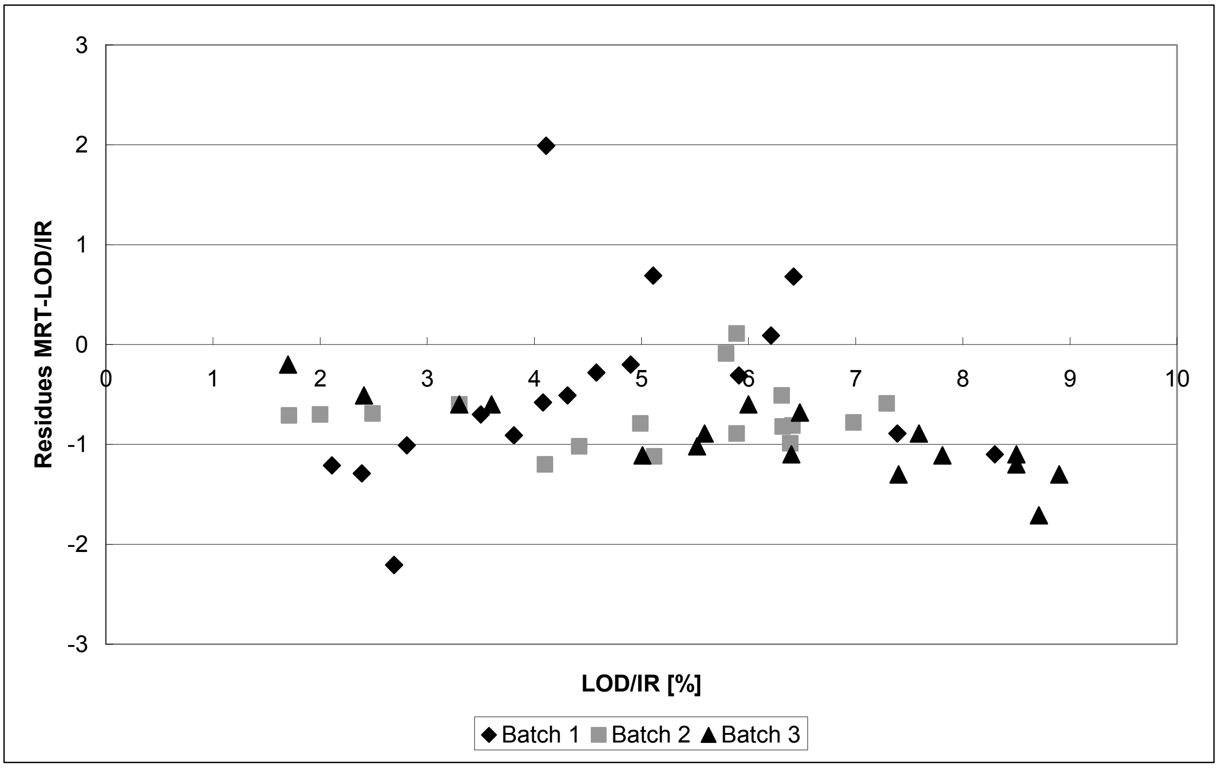

Fig. C-50: *Residues of MRT moisture [%] plotted against LOD/IR results of granule batches produced with increasing amount of partially pregelatinized maize starch (manufacturing device: GPCG 15).*

The residues of all three batches were found to be -0.1 to -1.5. Only the first granule batch, which contained the lowest fraction of PPMS, showed positive moisture residues in the range of 4–6.5 %. A stronger impact of increasing amounts of PPMS on MRT moisture measurement was not found. Due to the uniform behaviour of all three batches independently from the contained fraction of PPMS, it was assumed that a classification of the investigated PPMS / α-Lactose monohydrate relations to a superordinated calibration group is possible. A unique calibration for this formulation, covering all mass fractions of starch 1500, would be sufficient for the adjustment of the MRT sensor.

Furthermore, it was found that the third batch, containing the highest amount (40 %) of PPMS reached the highest moisture values (approximately 9 %) during granulation. This effect had already been observed for crospovidone (see chapter 9.1). Due to their swelling character, both substances increase the absorption of water molecules in the granules.

9.2.2 Granule properties

To investigate the influence of varying amounts of PPMS on granule properties, some granule characteristics were determined.

Granule flowability

As an important quality parameter, granule flowability was determined by a ring shear cell tester (see F 2.3.3).

As seen in Figure C-51, ff_c values considerably higher than 10 were found for all three batches. Independent of the contained fraction of PPMS, all three batches showed free-flowing characteristics. An impact of the increasing amount of PPMS on flow properties could not be identified.

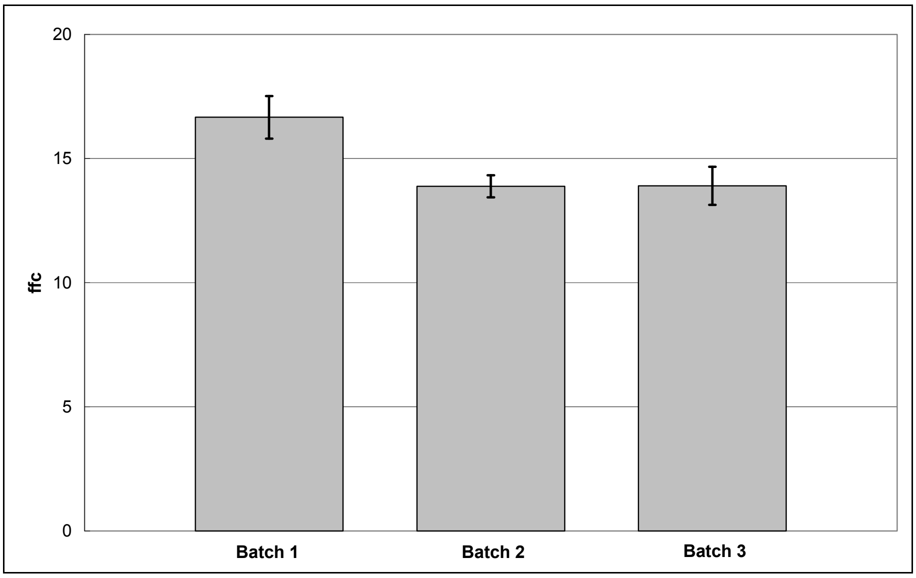

Fig. C-51: *Granule flowability of granule batches produced with increasing amounts of partially pregelatinized maize starch (n = 3, mean ± SD).*

Scanning electron microscopy

Granule surfaces were visualized by scanning electron microscopy (F 2.3.4). As seen in Figure C-52, granule surfaces showed similar characteristics. Differences were not apparent. All batches showed an irregular structure and individual particles of the ingredients could still be identified.

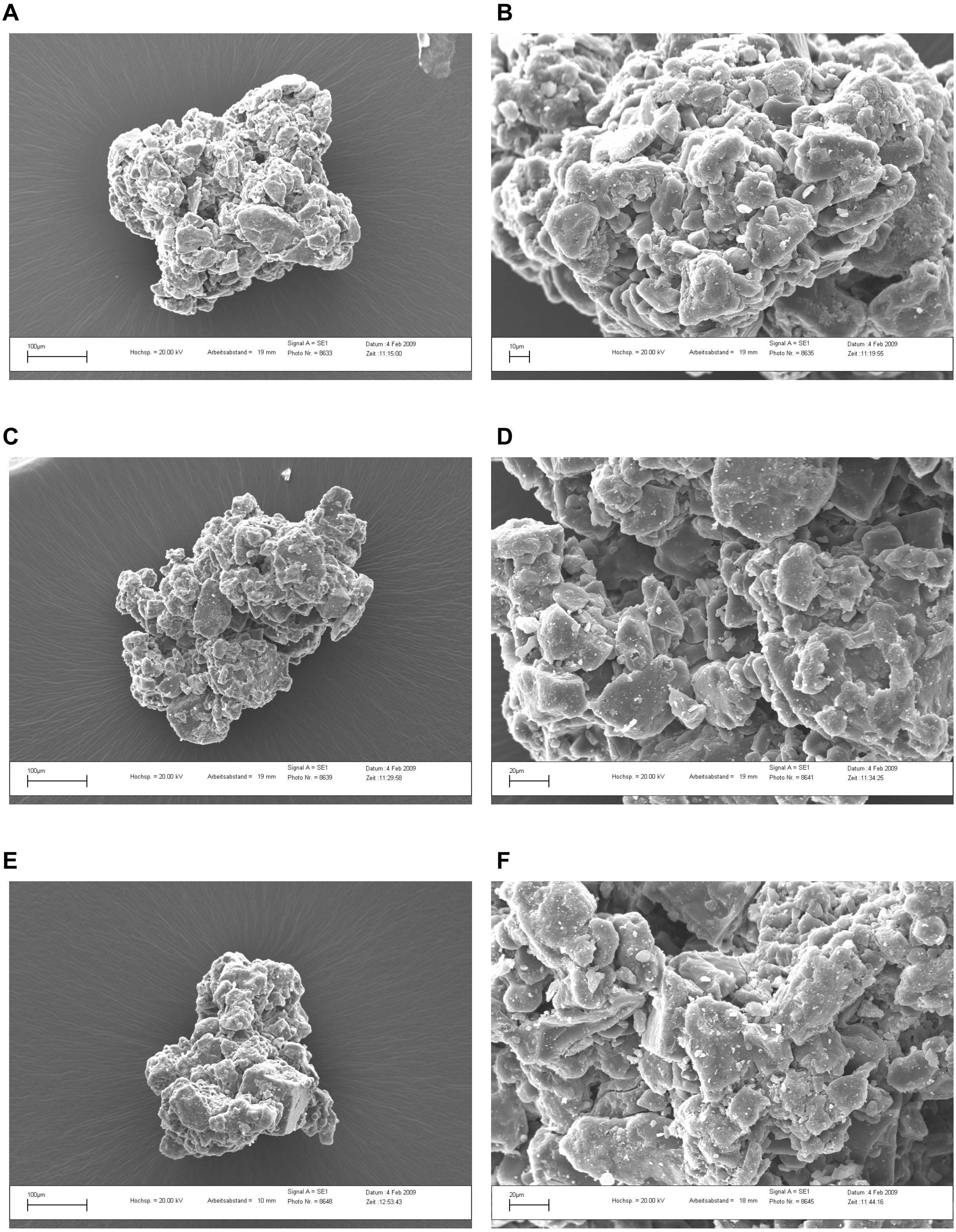

Fig. C-52: *Scanning electron micrographs of batches produced with increasing amounts of partially pregelatinized maize starch. A) 20 % PPMS, scale: 100 µm, adjusted magnification: 150x, B) 20 % PPMS, scale: 10 µm, adjusted magnification 500x, C) 30 % PPMS, scale: 100 µm, adjusted magnification 150x, D) 30 %PPMS, scale : 20 µm, adjusted magnification 500x, E) 40 % PPMS, scale: 100 µm, adjusted magnification 150x, F) 40 % PPMS, scale: 20 µm, adjusted magnification 500x*

9.3 Conclusion

To investigate the impact of excipients with swelling properties on MRT moisture measurement, two substances were used: crospovidone (CL PVP) and partially pregelatinized maize starch (PPMS). An impact on MRT signals for both substances was found. Granule properties were not found to be affected by the differing amount of the swelling substances.

During the production of granules containing higher amounts of CL PVP as swelling agent increasing deviations between MRT moisture measurement and the results of LOD/IR were observed. The impact on moisture measurement by MRT was significant. Consequently, the individual calibration for each amount of CL PVP was found to be mandatory. Due to CL PVP’s attribute to strongly absorb water molecules, higher moisture contents during the granulation process were obtained with increasing amounts of CL PVP.

For PPMS, the impact on MRT signals was found to be independent from the amount of partially pregelatinized maize starch. In fact a uniform influence was found. Therefore, the granule formulations may be summarized to one subordinated calibration group.

D Summary

The application of a microwave resonance (MRT) sensor system for the in-line control of fluidized bed processes, particularly with regard to the determination of the granule water content, was investigated.

This technique, already applied in a few industrial areas (e.g. timber industry) allows the density-independent determination of the moisture content of moving bulk solids. To use this measuring tool in pharmaceutical production processes, the existing sensor setup was re-engineered in accordance to the requirements of the current guidelines of Good Manufacturing Practice (cGMP), for instance by replacing materials. The implementation of the sensor system hydorpharm fbma® into two different fluidized bed granulators (Glatt GmbH) was successfully performed. The chosen mounting positions ensured a reliable and representative moisture measurement throughout the entire fluidized bed processes.

As MRT is an indirect measuring method, a calibration against a direct method for moisture determination was required. The determination of the loss on drying by infrared light (LOD/IR) and Karl Fischer titration (KF) were applied as reference methods. For both methods good correlations with the in-line results of MRT were obtained.
For most formulations, the base settings of the MRT sensor system were suitable for a reliable moisture control up to moisture contents of approximately 8.5 %. The classification of individual products with similar compositions to superordinated calibration groups was proven to be a valuable tool to decrease calibration complexity.

An impact on MRT moisture monitoring by substances with swelling characteristics was recorded. Due to the swelling and water absorbing properties of the excipient not all water molecules were detectable by MRT. Consequently, lower water contents were measured by MRT than by the reference methods. The size of the influence on the measuring results depended on the type of swelling agent, as well as its amount, contained in the formulation. For crospovidone (CL PVP), the impact on moisture measurement increased considerably with increasing amounts. Therefore, the classification of CL PVP containing products to superordinated calibration groups was not possible. In fact a sensor calibration was required for every amount of CL PVP. In contrast the impact of partially pregelatinized maize starch (PPMS) on MRT signals was uniform. Therefore, the generation of a calibration group was performed for PPMS containing granules.

The endpoint determination of the drying process of crystal-water-free as well as crystal-water-containing granules by MRT was proven to be reliable and reproducible. Due to the in-line moisture control, drying processes could be performed continuously instead discontinuously as it was the former practice. The processes were no longer interrupted for sample withdrawal and off-line moisture determination.
Hence, a considerably time saving of 75 % of the drying time was achieved. Continuous drying of the granules was associated with a reduction of various quality detracting influences.

A real-time process control throughout the entire wet granulation process of crystal-water-free as well as crystal-water-containing granules was enabled by MRT moisture monitoring. The measurement by MRT was proven to be reproducible. Furthermore, the results of the in-line (MRT) and off-line (LOD/IR, KF) methods were in a good agreement throughout the complete process run.
In one experiment, a deviating process course caused by a system failure was immediately identified at an early stage due to MRT monitoring. By performing in-line measurement of granule moisture, prompt intervention in a defective process became possible. Thus, product quality was ensured and the rejection of the affected batch avoided.

An impact of high moisture contents on the water determination by MRT was observed. With increasing water contents, the deviation between MRT and the reference methods increased. Above a product-specific threshold, MRT results were increasingly imprecise. The location of the threshold and the dimension of its impact on MRT signals depended on the respective granule composition. Within this study, the cause could not be entirely investigated and provided for calibration. Potentially, a revision of the evaluating software of the measuring system will be an approach for troubleshooting.

The simultaneous in-line monitoring of the temperature and a sensor signal, correlating with product density, performed by the MRT sensor system, enhanced process understanding considerably. Consequently, the efficiency of process control has improved.

The MRT sensor system was proven to be a valuable tool for the determination of the drying endpoint, and for moisture control of the entire wet granulation process. Product quality was ensured and process understanding increased. Using the novel MRT sensor system for in-line moisture control essential requirements of the PAT approach of the American Food and Drug Administration were met.

E Zusammenfassung

Die Anwendbarkeit eines Mikrowellen Resonanz (MRT) Sensorsystems für die in-line Steuerung von Wirbelschichtprozesses wurde mit besonderem Hinblick auf die Bestimmung des Wassergehaltes von pharmazeutischen Granulaten untersucht.

Diese Technik, die bereits in einigen Industriezweigen (z.B. der Holzindustrie) angewendet wird, erlaubt die dichteunabhängige Bestimmung des Feuchtegehaltes bewegter Schüttgüter. Um dieses Messwerkzeug in pharmazeutischen Produktionsprozessen nutzen zu können wurde die bisherige Sensorbauart überarbeitet. Gemäß den Anforderungen der aktuellen Leitlinien der guten Herstellpraxis (cGMP) wurden beispielsweise herkömmliche Materialien durch geeignete Baustoffe ersetzt. Die Implementierung des Sensorsystems hydorpharm fbma® wurde in zwei unterschiedlichen Wirbelschichtgranulatoren (Glatt GmbH) erfolgreich durchgeführt. Die gewählte Position stellte eine zuverlässige und repräsentative Feuchtemessung über die gesamten Wirbelschichtprozesse sicher.

Da es sich bei MRT um eine indirekte Messmethode handelt, war die Kalibrierung gegen eine direkte Methode zur Feuchtebestimmung erforderlich. Die Bestimmung des Trocknunsgverlustes mittels Infrarotlicht (LOD/IR) und die Karl-Fischer-Titration wurden als Referenzmethoden angewendet. Für beide Methoden wurden gute Korrelationen mit den in-line Ergebnissen des Mikrowellen Resonanz Sensors erzielt.
Für die meisten Formulierungen waren die Grundeinstellungen des MRT Sensorsystems für eine zuverlässige Feuchtekontrolle bis zu Feuchtegehalten von ungefähr 8,5 % geeignet. Die Zuordnung einzelner Produkte mit ähnlichen Zusammensetzungen zu übergeordneten Gruppen erwies sich als nützliches Instrument, um den Kalibrieraufwand zu verringern.

Ein Einfluss von Substanzen mit quellenden Eigenschaften auf die Feuchtemessung mittels MRT wurde festgestellt. Auf Grund der quellenden und Wasser absorbierenden Eigenschaften der Hilfsstoffe waren die Wassermoleküle für die Detektion mittels MRT nicht mehr vollständig verfügbar. Folglich wurden mittels MRT geringere Wassergehalte gemessen als mit den Referenzmethoden. Die Intensität des Einflusses auf das Messergebnis war sowohl von der Art des quellenden Agens als auch von dessen in der Formulierung enthaltenen Menge abhängig. Für Crospovidon (CL PVP) stieg der Einfluss auf die Feuchtemessung deutlich mit zunehmendem Anteil an CL PVP.
Demzufolge war die Zuordnung von CL PVP enthaltenen Produkten zu übergeordneten Kalibrierungsgruppen nicht möglich. Vielmehr war eine Kalibrierung für die jeweilige Menge an CL PVP erforderlich. Im Gegensatz dazu war der Einfluss von vorverkleisterter Maisstärke (PPMS) auf die MRT Signale gleichmäßig. Somit wurden PPMS-haltige Granulate zu einer übergeordneten Kalibrierungsgruppe zusammengefasst.

Die Endpunktbestimmung des Trocknungsprozesses erwies sich sowohl bei kristallwasserfreien als auch bei kristallwasserhaltigen Granulaten als zuverlässig und reproduzierbar. Durch die in-line Feuchtemessung konnten die Trocknungsprozesse kontinuierlich statt, wie bisher üblich, diskontinuierlich durchgeführt werden. Die Trocknungsprozesse mussten nicht mehr regelmäßig zur Probeentnahme und off-line-Feuchtebestimmung unterbrochen werden. Infolgedessen wurde eine beträchtliche Zeitersparnis von bis zu 75 % der Trocknungszeit erzielt. Die kontinuierliche Trocknung der Granulate war mit der Verringerung potentiell qualitätsbeeinträchtigender Einflüsse verbunden.

Eine Echtzeit Kontrolle wurde durch die MRT Feuchtemessung über den gesamten Feuchtgranulationsprozess sowohl von kristallwasserfreien als auch von kristallwasserhaltigen Granulaten ermöglicht. Die Messung mittels MRT erwies sich als reproduzierbar. Außerdem zeigten die Ergebnisse der in-line (MRT) und off-line (LOD/IR, KF) Methoden über den gesamten Prozessverlauf eine gute Übereinstimmung.
Ein abweichender Prozessverlauf, verursacht durch einen Systemausfall, wurde durch die MRT Überwachung bereits frühzeitig identifiziert. Durch die in-line Bestimmung der Granulatfeuchte war das Eingreifen in den fehlerhaften Prozess zeitnah möglich. Somit konnte die Produktqualität sichergestellt und die Vernichtung der entsprechenden Charge verhindert werden.

Auf die Wasserbestimmung mittels MRT wurde ein Einfluss von hohen Feuchten festgestellt. Mit zunehmendem Wassergehalt nahm die Abweichung der Messwerte von MRT und den Referenzmethoden zu. Das Vorhandensein eines kritischen Schwellenwertes verursachte diesen Effekt. Oberhalb des Scheitelpunktes waren die MRT Ergebnisse zunehmend ungenau. Die Lage des Schwellenwertes und das Ausmaß des Einflusses auf die MRT-Signale waren von der jeweiligen Granulatzusammensetzung anhängig. Im Rahmen dieser Arbeit konnte dieser störende Einfluss nicht vollständig behoben und in Kalibrierungen berücksichtigt werden. Möglicherweise bietet die Überarbeitung der Auswertesoftware des Messsystems einen Lösungsansatz.

Die gleichzeitige in-line-Überwachung von den Produktparametern Dichte und Temperatur, die vom MRT Sensor System durchgeführt wurde, erhöhte das Prozessverständnis beachtlich. Folglich konnte eine Effizienzsteigerung der Prozesskontrolle erreicht werden.

Das MRT Sensor System hat sich als wertvolles Instrument für die Bestimmung des Trocknungsendpunktes und der Feuchtekontrolle über den gesamten Prozess der Feuchtgranulierung bewährt. Die Produktqualität wurde sichergestellt und das Prozessverständnis nahm zu. Durch die Verwendung des neuartigen MRT Sensorsystems zur in-line-Feuchtekontrolle werden wesentliche Anforderungen des PAT Ansatzes der amerikanischen Food and Drug Administration erfüllt.

F Experimental part

1 Materials

1.1 Active pharmaceutical ingredients

Within this work steroid hormones were used as APIs. These APIs (see Table F-1) had in common a sensitivity to high moisture contents. Consequently, the in-line moisture control by MRT is a valuable tool to ensure product quality.
The API qualities, suppliers and exact proportions can not be shown due to confidential agreements.

Table F-1: *Active pharmaceutical ingredients used*

API group	Substance	Quality
I **Glucocorticoids**	Prednisolone	Ph. Eur. 6.0
	Prednisone	Ph. Eur. 6.0
	Triamcinolone	Ph. Eur. 6.0
II **Estrogens**	Estriole	Ph. Eur. 6.0
	Tibolone	Ph. Eur. 6.0
	Ethinylestradiole	Ph. Eur. 6.0
III **Gestagens and Anti-androgens**	Desogestrel	Ph. Eur. 6.0
	Gestodene	Ph. Eur. 6.5
	Medroxyprogesterone acetate	Ph. Eur. 6.0
	Chlormadinone acetate	JP 15
	Levonorgestrel	Ph. Eur. 6.0
	Cyproterone acetate	Ph. Eur. 6.0
IV **Others**	PW01*	Ph. Eur. 6.0

** Due to confidential agreements this API can not be named.*

1.2 Excipients

Table F-2 summarizes the excipients used within this work.

Table F-2: *Used excipients*

Excipient	Trade name	Supplier
Microcrystalline cellulose	Vivapur® 101	JRS Pharma, Rosenberg, Germany
	Avicel® PH 101	IMCD Deutschland, Köln, Germany
		FMC BioPolymer, Philadelphia, USA
α-Lactose monohydrate 100 mesh	Flowlac® 100	Meggle, Wasserburg, Germany
α-Lactose monohydrate 200 mesh	Granulac® 200	Meggle, Wasserburg, Germany
	Pharmatose® 200	DMV-Fonterra Excipients, Nörten-Hardenberg, Germany
Maize starch	C PharmGel	Cargill Deutschland GmbH, Krefeld, Germany
	-	Fagron GmbH & Co. KG, Barbüttel, Germany
Partially pregelatinized maize starch	Starch® 1500	Colorcon GmbH, Idstein, Germay
PW02*	-	BASF Ludwigshafen, Germany
Ascorbic acid	-	HeBei Welcome Pharmaceutical, Hebei Province, China
Magnesium stearate	Parteck® LUB MST	Merck KGaA, Darmstadt, Germany
Stearic acid	-	Mallinckrodt Baker Inc., Philipsburg, Germnay
Tartrazine	Corante Amarelo	Glatt GmbH, Binzen, Germany

** Due to confidential agreements this excipient can not be named.*

Table F-2: Used excipients (continuation)

Excipient	Trade name	Supplier
Disodium EDTA	-	Merck KGaA, Darmstadt, Germany
Povidone K 30	Kollidon 30®	BASF, Ludwigshafen, Germany
Crosslinked polyvinyl-pyrrolidone	Kollidon CL®	BASF, Ludwigshafen, Germany
Povidone 90	Kollidon 90F®	BASF, Ludwigshafen, Germany

1.3 Other substances

Within this work the following other substances were used (Table F-3).

Table F-3: Other used substances

Substance	Trade name	Manufacturer
Anolyte	Hydranal® Coulomat AG	Riedel-de Haën, Seelze, Germany
Catolyte	Hydranal® Coulomat EG	Riedel-de Haën, Seelze, Germany
Dried methanol	-	Merck KGaA, Darmstadt, Germany
Sodium tartrate dehydrate	-	Merck KGaA, Darmstadt, Germany
Pure nitrogen	-	Air Liquide, Krefeld, Germay

2 Methods

2.1 Manufacturing methods

2.1.1 Granulation

For all granulation and drying processes produced under GMP conditions, the fluidized bed granulator WSG 60 (FBE 250 R, Glatt GmbH, Binzen, Germany) was used. The batch size of the granulator is approximately 60 kg. A schematic drawing of the apparatus can be found in chapter C1 (Figure C-2). The inlet air used by the granulator could not be conditioned. Granulating fluids were applied by top spray. Due to the one-chamber filter system, the fluidisation was stopped when cleaning the filters.

Under experimental conditions the fluidized bed granulator GPCG 15 (Glatt GmbH, Binzen, Germany) was used. The maximum produced batch size of wet granules was 18 kg. Both granulators, WSG 60 and GPCG 15, operate with unconditioned inlet air and top spraying as well. The double-chamber filter system of GPCG 15 ensures in contrast to WSG 60 an uninterruptible process run, even when cleaning the filters by vibration.

The granule batch of product B (see chapter C 4.1) was produced in the V-blender 2 cuft (Patterson-Kelley, Pennsylvania, USA). Rotation speed was approximately 20 rpm. After 2 minutes the chopper was switched on for 1 minute.

The granule batches of product C, described under chapter C 4.1, were produced in the high-shear mixer FM-Vd-267 (Powrex, HypoKen, Japan). Afterwards the wet granules were passed through a 5 mm wet sieve (GS 180, Glatt GmbH, Binzen, Germany).

The following tables summarize process conditions of the fluidized bed processes of all produced batches for each product. During the processes the respective parameters were checked and noted every 15 minutes.

Product A

Manufacturing device: WSG 60
State: GMP

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	20-69	19-38	1000-1137	
Spraying	45-69	33-40	1147-1503	300
Drying	60-66	32-40	1080-1413	

Product B

Manufacturing device : WSG 60
State: GMP

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Drying	50-74	34-38	1303-1355	

Product C

Manufacturing device : GPCG 15
State: technical

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	60-64	33-45	1000-1700	
Spraying	58-62	22-45	850-1700	136-310
Drying	45-65	22-39	840-1700	

Product D

Manufacturing device: WSG 60
State: GMP

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	20-53	20-37	978-1200	
Spraying	50-73	30-38	968-1265	280-320
Drying	59-73	33-36	1166-1190	

Product E

Manufacturing device: WSG 60
State: GMP

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	20-75	20-37	914	
Spraying	47-74	31-37	1053-1176	320
Drying	50	33	1156	

Product F

Manufacturing device: WSG 60

State: GMP

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	20-48	20-37	914-1103	
Spraying	47-82	30-37	1118-1350	280-320
Drying	56-79	33-35	1151-1258	

Product G

Manufacturing device: WSG 60

State: GMP

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	28-87	21-37	967-1176	
Spraying	46-79	33-37	1048-1217	320
Drying	76	33	1176	

Product H

Manufacturing device: WSG 60

State: GMP

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	21-80	20-37	1023-1164	
Spraying	58-68	32-37	1105-1187	320
Drying	61	32	1187	

Product I

Manufacturing device: WSG 60

State: GMP

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	22-60	21-37	1032-1103	
Spraying	60-75	35-37	1089-1302	350
Drying	50-55	34-38	1303-1330	

Product J

Manufacturing device: GPCG 15

State: technical

Constant spraying rate

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	70-72	34-40	1100	
Spraying	62-70	24-34	1100	320
Drying	62	24-40	1100	

Varying spraying rate

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	74	48	1100	
Spraying	62-70	26-46	1100	100-350
Drying	62	26-48	1100	

Product K

Manufacturing device: GPCG 15
State: technical

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	70-74	37-47	1100	
Spraying	62-64	24-41	1100	255-350*
Drying	62	26	1100	

**increase of the spraying rate at predefined time points: after a process time of 21 min first increase from 255 g/min to 320 g/min, second increase to 350 g/min after a process time of 29 min*

Product L

Manufacturing device: GPCG 15
State: technical

Process phase	Inlet air temperature [°C]	Product temperature [°C]	Inlet air volume [m³/h]	Spraying rate [g/min]
Preheating	64-74	36-45	1100	
Spraying	62-72	24-38	1100	300
Drying	62	25-45	1100	

2.1.2 Blending of granules

Prior to compression the dried granules were blended in a 20 cuft V-blender (Patterson-Kelley, Pennsylvania, USA) with the respective lubricant. For product D the lubricant was 820 g stearic acid, for product F 330 g magnesium stearate. Blending was performed for 15 min at 5 rotations per minute. The chopper was switched on for 10 seconds.

2.1.3 Compression of granules

For compression of granules a rotary press type P 3000 Klimatex (Fette GmbH, Schwarzenbek, Germany) was used. The tablet press consists of 60 punches for compression. For product F punch size was 12 mm (specified tablet mass: 100 mg) and for product D 6 mm (specified tablet mass: 80.5 mg). The compression speed was approximately 170,000 tablets per hour for product D and 198,000 tablets per hour for product F.

2.2 Methods of moisture determination

2.2.1 Sampling

To compare the different methods of moisture determination samples were withdrawn throughout the entire fluidized bed processes. Sampling was performed using the sample probe of the respective fluidized bed granulator. The probe was located in the product bowl at the same height as the MRT sensor system (see Figure C-3). Thus, comparable conditions were guaranteed. Sampling was performed periodically directly prior to the cleaning vibrations of the fine particle filters. The quantity of each sample was approximately 4 g.

2.2.2 Loss on drying by infrared light exposure

For the determination of the loss on drying by infrared light two different devices were used. Under GMP conditions the measurement was performed using the heat balance MA 45 Moisture Analyzer® (Sartorius AG, Göttingen, Germany). The temperature was set for all products, to 80 °C, except for product A (100°C). The endpoint determination was performed in the automatic mode.

The moisture content of samples withdrawn throughout technical granulation processes was determined using the heat balance LF 16 Moisture Analyzer® (Mettler Toledo GmbH, Gießen, Germany). In this case the temperature was set to 70 °C. The endpoint determination was performed in the automatic mode as well.

2.2.3 Karl Fischer titration

The moisture content of granule samples was measured using the Moisture Meter® CA-100 with the dry heat oven (vaporizer) VA-100 (Mitsubishi Chemical Industries Limited, Tokyo, Japan). The operating medium was Hydranal® Coulomat AG, Hydranal® Coulomonat CG and dried methanol. At the beginning of each measuring cycle and in the following after every fifth measurement, the water content of approximately 15 mg (exactly weighed) di-sodiumtartrate-dihydrate (water content 15.66 %) was determined in triplicate in order to verify the titration results. The results were specified to be in the range between 15.46 % and 15.86 %, or the measurements settings had to be adjusted and measurements had to be repeated.

The granule sample to be tested was weighed in an aluminium crucible using the analytical balance AT261 Delta Range (Mettler Toledo GmbH, Gießen, Germany). Afterwards the moisture was vaporized by heating at 170 °C and led into the coulometric measuring cell by a nitrogen flow (250 ml/min). The endpoint determination was performed automatically.

2.2.4 Microwave resonance technology

For in-line moisture monitoring in fluidized bed processes, the microwave resonance sensor system hydorpharm® fbma (AMS Advanced Microwave Systems GmbH, Elmshorn, Germany) was used. The sensor system suitable for pharmaceutical application was developed within this study (see chapter C 1). Due to the application in fluidized bed processes the sensor head was constructed as a stray field resonance sensor.

The generated electromagnetic stray field extends into the product space. In order to compensate covariates an independent reference unit was incorporated in the sensor. The operating frequency of the stray field resonance sensor was 2.5 GHz, which is a free ISM band. By using this frequency, heat losses due to dissipation and interfering ionic influences were excluded (see chapter B 5). Due to the fact that the MRT sensor works at a very low energy level of less than 10 mW, warming of the monitored product does not occur.

As the signals from the microwave resonance sensor depend on the absolute temperature in general, the temperature was measured directly under the sensor's surface by a PT 100 thermo sensor. According to Knöchel (2007), the influences of the temperature on MRT sensors are often negligible. As the temperature range of the performed fluidized bed processes was very narrow, the temperature signals were not used to correct the MRT results.

Prior to each measuring process, the blank value of the unstressed sensor was determined.

The received measuring values for moisture, density and temperature were analyzed electronically and evaluated in real-time by the provided software MWF-Standard (AMS Advanced Microwave Systems GmbH, Elmshorn, Germany). All settings and requirements are conducted in the software. The measurements were carried under software control.

Furthermore, the software provides the opportunity of incorporating results of reference measurements and using them for calibration purposes. Of particular importance is the possibility of saving product-specific data. Measuring data as well as calibration curves may be incorporated and saved for each product. Afterwards these data are available for all subsequent measurements. Accordingly, the complexity of calibration process can be considerably reduced.

Calibration and adjustment of the MRT sensor system

As microwave resonance technology is an indirect method for the determination of water content, calibration against a suitable reference method is required. Within this study the MRT sensor was used for the monitoring of granulation processes of highly active solid formulations, where the mass fraction of the active pharmaceutical ingredients (API) was comparatively low. Therefore, the basic idea was to constitute superordinated groups in accordance with the composition of the products. That means that products with a similar composition were summarized in one calibration group.

The aim of this approach was to simplify calibration. Instead of calibrating the MRT sensor for a specific product, calibration should be performed for the whole group. Prior to manufacturing a new product, it was controlled whether the product could be classified to an existing group. Otherwise a new calibration group was generated. Furthermore, it may happen that in the course of time with increasing product numbers per group, a subdivision of a superordinated group became necessary. Table F-4 provides a summary about group formation.

Table F-4: *Superordinated calibration groups*

Number	Main excipients	Granulating fluid	Number of products
1	α-Lactose monohydrate	Kollidon K 30, purified water	2
2	α-Lactose monohydrate, Maize starch	Maize starch, purified water	3
3	MCC	Kollidon F 90, purified water	1
4	α-Lactose monohydrate, PPMS	Kollidon K 30, purified water, partially APIs	6
5	α-Lactose monohydrate, Maize starch	Kollidon K 30, purified water	3
6	α-Lactose monohydrate, MCC	Kollidon F 90, purified water	1

It was hindering that no specified, universally valid method for the determination of the water content of solids is available. In order to identify a suitable reference method, it is complicating that each method detects different water types (see chapter B 4). A direct comparison of the results obtained by the different methods is not possible in all cases. Furthermore, deviating moisture results for the same sample may follow as most methods are off-line methods for moisture determination, and therefore require sample withdrawal, packaging and preparation prior to the measurement. During this time period, properties of the sample may change due to environmental influences. In contrast, microwave resonance technology enables the in-line measurement of the granule water content within ongoing processes.

Within this study, the determination of the loss on drying by infrared light (LOD/IR) and Karl Fischer titration (KF) were used as independent reference methods for the adjustment and calibration of the sensor. However, it is nondistinctive which method is superior and should be used for calibration of the sensor. While the LOD/IR method mainly detects water molecules weakly bound to the granule's surface, but not strongly bound or crystal water, KF determines both, chemically as chrystallographically bound water.

This depends on measuring conditions as only water molecules vaporized from the granules are measured by the KF method. In contrast, using microwave resonance technology all types of water, except chrystallographically bound water should be detected. For the determination of crystal-water, the frequency and energy of the applied microwaves are not able to translate or rotate water molecules in crystals.

Therefore, it was decided to perform calibration of the sensor system by cross-over adjustment referring to both reference methods. The moisture tracks of many granulation processes of each product were recorded in-line by MRT. The first produced batches were used as training batches. According to the results of the training batches, calibration was applied for subsequently produced test batches. The composition of the test batches was the same as for the training batches and wet granulation was performed under comparable conditions. The quantity of training and test batches depends on the total numbers of produced batches. Calibration was performed on at least ten samples.

To compare the MRT moisture values with a reference method, samples were withdrawn throughout the entire process of each batch (see chapter F 2.2.1). Afterwards the samples were analyzed off-line by LOD/IR and KF.

In order to evaluate the data, the correlation coefficient and the slope of the regression line were determined by plotting the MRT results of the training batches against the results of the respective reference method.

Furthermore, statistical variables such as Pearson’s correlation coefficient (Equation F-1) and covariance (Equation F-2) were calculated.

$$r = \frac{\sum_{i=1}^{n} (x_i - \overline{x})(y_i - \overline{y})}{\sqrt{\sum_{i=1}^{n} (x_i - \overline{x})^2 \cdot \sum_{i=1}^{n} (y_i - \overline{y})^2}} \qquad \text{(Eq. F-1)}$$

$$\mathrm{cov}_{xy} = \frac{1}{n-1} \sum_{i=1}^{n} (x_i - \overline{x})(y_i - \overline{y}) \qquad \text{(Eq. F-2)}$$

n	*number of measurements*
x_i	*measurement i using method A*
$\overline{x}$	*mean of measurements using method A*
y_i	*measurement i using method B*
$\overline{y}$	*mean of measurements using method B*

The results of the statistical analysis of the training batches were used to apply calibration retrospectively on MRT sensor signals. For subsequently produced test batches, the respective calibration was implemented in the software.

2.3 Characterisation methods

2.3.1 Sample division

To verify a representative sample the granules were divided in eight parts using the sample divisor PT (Retsch GmbH, Haan, Germany).

2.3.2 Sieve analysis

The particle size distribution of granules was performed by vibrating sieving analysis. Using the sieving machine Vibrio AS 200 Control (Retsch GmbH, Haan, Germany) granules were sieved for 4 min with an amplitude of 1.5 mm. Sieves with mesh sizes of 80, 125, 200, 315, 500, 800, 1000 and 1250 µm were used. The masses of the tested granules as well as the residue masses on individual sieves were determined by the analytical balance Mj-3000 (YMC Europe GmbH, Dinslaken, Germany).

2.3.3 Granule flowability

Granule flowability was determined using the ring shear cell tester RST-01.pc combined with the software package RST-CONTROL 95 (Schulze Schuettgutmesstechnik, Wolfenbuettel, Germany). The measurements were performed under computer-control. A schematic illustration of the measuring apparatus is displayed in Figure F-1.

The ring shear cell tester consists of a bottom ring with a checkered structure and a top cover with baffles. The sample to be tested was placed into the bottom ring. Preshearing was performed with a predefined normal load of 5 kPa until stationary flowing was reached (at a constant normal load a constant shear stress was obtained). Subsequently, the sample was discharged from the normal load automatically. During this measurement phase the sample was solidified in order to obtain a reproducible and defined stage. The same operating conditions are provided for each measurement.

Shearing was performed at four different normal loads (1,2,3 and 4 kPa). At a particular shear stress, flowing of the granule sample started. Between the individual measurements the sample was solidified again at a normal load of 5 kPa.

In order to exclude influences of the measurement on the sample, at the end of a measuring cycle the first run with a normal load of 1 kPa was repeated. Three sample of each granule batch were measured.

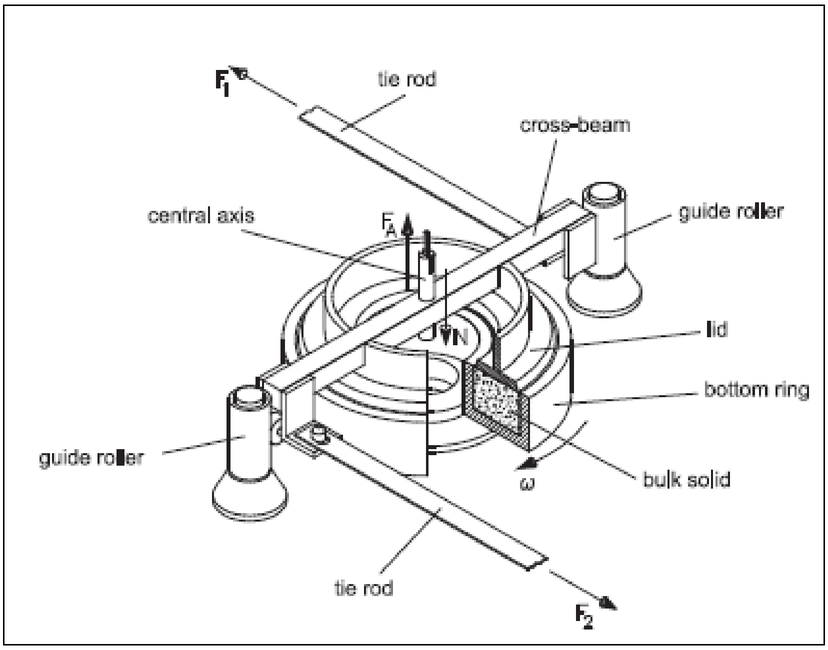

Fig. F-1: *Schematic illustration of the ring shear cell tester [Schulze 1996].*

As parameter for flow properties, the flowability function (ff_c) was used. It is defined as the ratio of consolidation stress (σ_1) and unconfined yield strength (σ_c) (Equation F-3):

$$ff_c = \frac{\delta_1}{\delta_c} \qquad \text{(Eq. F-3)}$$

ffc	*flowability function*
σ_1	*consolidation stress [Pa]*
σ_c	*unconfined yield strength [Pa]*

The ff_c values were automatically calculated by the respective software. With increasing ff_c values granule flowability improves (see Table F-5).

Table F-5: *Classification of bulk flow properties according to Jenike (1964).*

ff_c value	**flow behaviour**
$ff_c < 1$	non flowing
$1 < ff_c < 2$	very cohesive
$2 < ff_c < 4$	cohesive
$4 < ff_c < 10$	easy-flowing
$10 > ff_c$	free-flowing

2.3.4 Scanning electron microscopy

The scanning electron microscope Leo 1430 VP (Leo Electron Microscopy, Cambridge, UK) was used to visualize granule surfaces. Prior to electron microscopic investigation, the granule samples were gold sputtered for 180 sec under argon atmosphere using the Agar Manual Sputter Coater B7340 (Agar Scientific, Stansted, UK). Scanning electron micrographs were taken under vacuum with a working voltage of 20kV.

2.3.5 Tablet breaking strength

Using a breaking strength tester (TBH 220 TD, ERWEKA® GmbH, Heusenstamm, Germany) tablet breaking strength was determined during compression every 20 minutes in triplicate.

2.3.6 Tablet thickness

Tablet thicknesses were determined using a digital calliper (Hogetex Deutschland GmbH, Nieder-Olm, Germany). During compression, the test was performed every 20 minutes in triplicate.

2.3.7 Tablet mass

An analytical balance (SL220M, Bizerba GmbH & Co. KG, Balingen, Germany) was used for the determination of tablet mass. The test was performed during compression every 20 minutes. Sample size was 3x10 tablets at each sampling time point. The mean was calculated using 10 tablets in each case.

2.3.8 Uniformity of mass

Using the check weigher UCW4 combined with the CGS control balance UCW 4 (CGS GmbH, Hamburg, Germany) the mass uniformity of tablets was determined (Ph. Eur. 2.9.5 “Uniformity of mass of single-dose preparations”). The tests were performed every four hours. Due to the 60 compression punches, the sample size was 60 tablets in each case (instead of 20 as specified in Ph. Eur.). Not more than two of the individual masses were allowed to deviate from the required mass by more than 7.5 %. No sample was allowed to deviate more than 15 % from the required mass.

2.3.9 Friability of tablets

Friability of tablets was determined using the friability tester TA 200 (ERWEKA® GmbH, Heusenstamm, Germany). According to the European Pharmacopoeia (2.9.7 “Friability of uncoated tablets”) sample size of whole tablets was as near as possible to 650 mg. Rotations of the measuring drum were 25 rotations per minute. After 100 rotations tablets were removed from the drum and weighed using the analytical balance AT261 Delta Range (Mettler Toledo GmbH, Gießen, Germany). The maximum loss of mass should not be greater than 1.0 %, calculated from a single test at the beginning of each compression day.

2.3.10 Disintegration time of tablets

Disintegration time of tablets was determined according to Ph. Eur. 6.0 monograph 2.9.1 by the ZT71 device (ERWEKA® GmbH, Heusenstamm, Germany). The specified disintegration time is 15 minutes. The test was performed at the beginning of each compression day on 6 samples. The temperature of the test medium (demineralised water) was 36-38 °C.

G Bibliography

Augsburger L.L., Vuppala M.K., Theory of granulation, In: Parik D.M., Handbook of pharmaceutical granulation technology. Marcel Dekker New York (1997) 7-8

Bauer K.H., Frömming K.-H., Führer C., Lehrbuch der Pharmazeutischen Technologie, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart (1999) 305-306

Bender H., Hiob M., Kamm T., Peither T., Schwarzat U., Unverferth E., Wecherle B., GMP-Berater Technik, Maas & Peither – GMP Verlag Schopfheim (2007)

Berntsson O., Zackrisson G., Östling G., Determination of moisture in hard gelatin capsules using near-infrared spectroscopy: applications to at-line process control of pharmaceutics, J Pharm Biomed Anal 15 (1997) 895-900

Börste G., Optimierung der Feuchteregelung bei der MDF-Herstellung-Maß aller Dinge, MDF-Magazin 10 (2007) 78-79

Brokmann T., Infrarot-Meßverfahren, In: Materialfeuchtemessung Grundlagen – Meßverfahren – Applikationen – Normen, Expert-Verlag Renningen-Malmsheim (1997) 203-216

Brosio E., Conti F., Lintas C., Sykora S., Moisture determination in starch-rich food products by pulsed nuclear magnetic resonance, J Food Technol 13 (1978) 107-116

Buchanan B.R., Baxter M.A., Chen T.S. Qin X.Z., Robinson P.A., Use of near-infrared spectroscopy to evaluate an active in a film coated tablet, Pharm Res 13 (1996) 616-621

Bundesinstitut für Arzneimittel und Medizinprodukte, PAT – Ein Paradigmenwechsel in der Arzneimittelherstellung und Qualitätskontrolle, www.bfarm.de/cln_030/nn_1199184/DE/Arzneimittel/2_zulassung/zulVerfahren/pharmQual/pat/pat-node.html-nnn=true

Buschmüller C., Wiedey W., Döscher C., Dressler J., Breitkreutz J., In-line monitoring of granule moisture in fluidized-bed dryers using microwave resonance technology, Eur J Pharm Biopharm 69 (2008) 380-387

current EU Guildelines of Good Manufacturing Practice, European Comission Volume 4 (2003)

Daschner F., Knöchel R., Taute W., Döscher C., Feuchte- und Dichtemessung Präzise und zerstörungsfreie Bestimmung in Echtzeit zur Kontrolle von Prozessen, GIT Labor-Fachzeitschrift 7 (2006) 2-4

Döscher J., Auf der richtigen Wellenlänge Präzise Feuchtemessung per Mikrowelle im MDF-Produktionsprozess, Sonderdruck MDF-Magazin (1999) 86-87

Döscher J., Die Dichte ist egal, Process (2002) 44-45

El Hagrasy A.S., Chang S-Y., Desai D., Kiang S., Raman spectroscopy for the determination of coating uniformity of tablets: assessment of product quality and coating pan mixing efficiency during scale-up, JPI 1 (2006) 37-42

European Pharmacopoeia 6, Various monographies, Deutscher Apotheker Verlag Stuttgart (2008)

Glatt GmbH, Method for monitoring and/or controlling and regulating a granulation, agglomeration, instantization, coating and drying process in a fluidized layer or a fluidized bed by determining product moisture, and device for carrying out said method, EP0970369B1 (1997)

Faure A., York P., Rowe R.C., Process control and scale-up of pharmaceutical wet granulation processes: a review, Eur J Pharm Biopharm 52 (2001) 269-277

Food and Drug Administration, Pharmaceutical cGMPs for the 21st Century-A risk based approach, Final report, (2004)
http://www.fda.gov/Cder/gmp/gmp2004/GMP_finalreport2004.htm

Food and Drug Administration, Process Analytical Technology Initiative, Guidance for Industry PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance, (2004) http://www.fda.gov/Cder/OPS/PAT.htm

Goebel S.G., Steffens K.-J., On-line measurement of moisture and particle size in the fluidized-bed process with near-infrared spectroscopy, Pharm Ind 60 (1998) 889-895

Hinz D. C., Process analytical technologies in the pharmaceutical industry: the FDA's PAT initiative, Anal. Bioanal. Chem. 384 (2006) 1036-1042

ICH expert working group, ICH Quality guideline Q 8 Pharmaceutical Development (2003)

ICH expert working group, ICH Quality guideline Q 9 Quality Risk Managment (2003)

Jenike A.W., Storage and flow of solids. Bulletin of the University of Utah No 123 (1964), Engineering Experiment Station, University of Utah Salt Lake City

Johnson P., A moisture control system for animal feed production, Feed compounder (2007) 26-27

Jong de J.A.H., Tablet properties as a function of the properties of granules made in a fluidized bed process, Powder Technol 65 (1991) 293-303

Kalinski J., Einige Probleme der industriellen Feuchtemessung mit Mikrowellen, TIZ (Fachberichte) 103 (1979) 145-153

Kalinski J., Some possible of technological quality control on the basis of the laboratory measurements of materials, Proc. of the international symposium of metrology for quality control, Tokyo (1984) 31-34

Klein A., Untersuchung der dielektrischen Eigenschaften feuchter Steinkohle im Hinblick auf die Anwendbarkeit des Mikrowellenfeuchtemeßverfahrens zur Wassergehaltsbestimmung, Dissertation RWTH Aachen (1978)

Knöchel R., Taute W., Döscher C., Microwave apparatus for moisture measurement, with temperatur compensation, EP 1331476B1 (2003)

Knöchel R., Taute W., Döscher C., Stray field ring resonator and a novel through guide resonator for precise microwave moisture and density measurements, Meas Sci Technol 18 (2007) 1061-1068

Kuhn K., Kernresonanzmessung und Wasseraktivitätsbestimmung zur Aufklärung des Trocknungsverhaltens von Kartoffeln, Dissertation University Hamburg (1986)

Kupfer K., In: Materialfeuchtemessung Grundlagen – Meßverfahren – Applikationen – Normen, Expert-Verlag Renningen-Malmsheim (1997)

Leuenberger H., New trends in the production of pharmaceutical granules: batch versus continuous processing, Eur J Pharm Biopharm 52 (2001) 289-296

Mannhardt J., Selbstreinigendes Beobachtungsfenster macht die Detektion sicher, Process (2007) www.process.vogel.de/msr_automatisierung/messtechnik/sensoren/articles/60932

Mattes R., Root D., Birkmure A., In-line process analysis of residual moisture in a fluid bed granulator-dryer using NIR spectroscopy, Spectroscopy (2005)

Melichar M., Untersuchungen zur Feuchtemessung an pharmazeutischen Hilfsstoffen mit Hilfe der Mikrowellen-Resonanzspektroskopie, Dissertation University Bonn (2007)

Merckle P., Kovar K.A., Assay of effervescent tablets by near-infrared spectroscopy in transmittance and reflectance mode: acetylsalicylic acid in mono and combination formulations, J Pharm Biomed Anal 17 (1998) 365-374

Methfessel J., Roy J.-R., A pratical approach to PAT implementation, Pharm Tech Eur 18 (2006) 24-31

Müller J., Kleinebudde P., Thies J., Uerpmann C., Raman spectroscopy as PAT tool in film coating, Abstract Achema (2009) https://ssl.achema.de/index.php?id=116220&tagung=9&file=8015&site=achema2009&lang=en&path=1%25252C79095

NDC, PharmaView^{TM} Real-time Process Moisture Visualization with end-point determination, Booklet (2007)

Peters J., Spielau M., Die coulometrische Karl-Fischer Titration Einfache und empfindliche Methode zur Wasserbestimmung; GIT Labor-Fachzeitschrift 10 (2007) 824-827

Quadir A., Kolter K., A Comparative Study of Current Superdisintegrants, (2006) http://pharmtech.findpharma.com/pharmtech/Excipients/A-Comparative-Study-of-Current-Superdisintegrants/ArticleStandard/Article/detail/378399

Rantanen J., Jørgensen A., Räsänen E., Luukkonen P., Airaksinen S., Raiman J., Hänninen K., Antikainen O., Yliruusi J., Process analysis of fluidized bed granulation, AAPS Pharm Sci Technol 2 (2001) 21

Schmidt-Lehr S., Moritz H.-U., Jürgens K. C., Online-Kontrolle der Partikelgröße während einer Wirbelschichtgranulation, Pharm Ind 69 (2007) 478-484

Schæfer T., Wørts O., Control of fluidized bed granulation III, Arch Pharm Chem Sci 6 (1978) 69-82

Schinzinger O., Schmidt P.C., Comparison of the granulation behaviour of three different excipients in a laboratory fluidized bed granulator using statistical methods, Pharm Dev Technol 10 (2005) 175-188

Schulze D., Flowability and time consolidation measurements using a ring shear cell tester. Powder handling and processing 8 (1996) 221-226

Serno P., Kleinebudde P., Knop K., Granulieren Grundlagen, Verfahren, Formulierungen, ECV Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH Aulendorf (2007)

Shangraw R., Wallace J., Bowers F., Morphology and functionality in tablet excipients for direct compression, Pham Technol 5 (1981) 44-60

Tabacco Journal, Moisture measurement goes electromagnetic, Tabacco Journal (2002) 56-58

Trafford A.D., Jee R.D., Moffat A.C., Graham P., A rapid quantitative assay of intact paracetamol tablets by reflectance near-infrared spectroscopy, Analyst 124 (1999) 163-170

Watano S, Terashita K, Miyanami K. Determination of Endpoint with a complex granulation applying infrared moisture sensor, Chem Pharm Bull 39 (4) (1991) 1013 – 1017.

Watano S, Yamamoto A, Miyanami K. Effects of operational variables on the properties of granules prepared by moisture control method in tumbling fluidized bed granulator, Chem Pharm Bull 42 (1) (1994) 133 – 137.

Watano S, Takashina H, Sato Y, Yasutomo T, Miyanami K., Measurement of moisture content by IR sensor in fluidized bed granulation. Effects of operating variables on the relationship between granule moisture content and absorbance of IR spectra, Chem Pharm Bull 44 (6) (1996) 1267 – 1269.

Wernecke R., Industrielle Feuchtemessung, VIELEY-VCH Verlag GmbH & KGaA Weinheim (2003)

White J.G., On-line moisture detection for a microwave vaccum dryer, Pharm Res 11 (1994) 728-732

Wildfong P:L:, Samy A.-S., Corfa J., Peck G.E., Morris K.R., Accelerated fluid bed drying using NIR monitoring and phenomenological modelling: method assessment and formulation suitability, J Pharm Sci 91 (2002) 631-639

Wolter B., Krus M., Moisture measuring with Nuclear Magnetic Resonance (NMR), In: Electromagnetic Aquametry, Springer Verlag Berlin Heidelberg (2005)

H List of publications, oral and poster presentations

Buschmüller C., Wiedey W., Döscher C., Plitzko M., Breitkreutz J., In-line monitoring of granule moisture and temperature throughout the entire fluidized bed granulation process using microwave resonance technology, Pharm Ind (2009) in press

Buschmüller C., Wiedey W., Döscher C., Dressler J., Breitkreutz J., In-line monitoring of granule moisture in fluidized-bed dryers using microwave resonance technology, Eur J Pharm Biopharm 69 (2008) 380-387

In-line monitoring of granule properties in fluidized-bed granulation processes using a novel PAT tool; oral presentation, 19th Helsinki Drug Research (2008), Helsinki

In-line monitoring der Granulatfeuchte im Wirbelschicht- Trocknungsprozess mit Hilfe der Mikrowellen-Resonanz-Technologie als neue PAT Methode; oral presentation, DPHG Jahrestagung (2007), Erlangen

In-line measurement of granule water content in fluidized bed dryer using microwave resonance technology as a novel PAT tool; oral presentation, 2nd European Congress on Life Science Process Technology (2007), Nürnberg

In-line monitoring of granule properties in fluidized-bed granulation processes using microwave resonance technology as a novel PAT tool; poster presentation, Workshop “Hands-on implementation of Process Analytical Technology in Production Processes” (2008), Gent

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Selbsttätigkeitserklärung

Die vorgelegte Dissertation habe ich selbsttätig ohne unerlaubte Hilfe angefertigt.
Die Dissertation wurde weder in der vorgelegten noch einer ähnlichen Form bei einer anderen Institution eingereicht.
Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den 15. Mai 2009

C. Buschmüller

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