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NEAR INFRARED AND RAMAN SPECTROSCOPY FOR THE IN-PROCESS MONITORING OF PHARMACEUTICAL PRODUCTION PROCESSES

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Abstract

Within the Process Analytical Technology (PAT) framework, it is of utmost importance to obtain critical process and formulation information during pharmaceutical processing. Process analyzers are the essential PAT tools for real-time process monitoring and control as they supply the data from which relevant process and product information and conclusions are to be extracted. Since the last decade, near infrared (NIR) and Raman spectroscopy have been increasingly used for real-time measurements of critical process and product attributes, as these techniques allow rapid and nondestructive measurements without sample preparations. Furthermore, both techniques provide chemical and physical information leading to increased process understanding. Probes coupled to the spectrometers by fiber optic cables can be implemented directly into the process streams allowing continuous in-process measurements. This paper aims at reviewing the use of Raman and NIR spectroscopy in the PAT setting, i.e. *during* processing, with special emphasis in pharmaceutics and dosage forms.

1. Introduction

The Food and Drug Administration's (FDA) Process Analytical Technology (PAT) initiative (FDA, 2004) forms the basis of the pharmaceutical Good Manufacturing Practice (GMP) rules for the 21st century (Hinz, 2006). Because the pharmaceutical industry is highly regulated, final products must meet very stringent specifications. However, this does not mean that pharmaceutical processes are optimized. Conventional pharmaceutical manufacturing is generally accomplished using batch processing with off-line time-consuming and less efficient laboratory testing conducted on randomly collected samples to evaluate quality. The processes themselves are not fully understood and are often inefficient black-boxes. Limited relevant information is mainly obtained after the process, making process control difficult which can result in batch losses. The ultimate goal of PAT is a better fundamental scientific understanding of manufacturing processes (i.e., the process should not be a black box system). One of the most important statements within the PAT concept is that '*quality should not be tested into products; it should be built in'.* PAT should therefore play a crucial role in design, analysis, and control of manufacturing processes based on timely in-line, on-line and at-line measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials, with the goal of ensuring final product quality (EUFEPS QbD and PAT Sciences Network, 2010). It is thus aimed to obtain real-time information of all critical process aspects and to guide processes towards their desired state, hence ensuring the quality of each end product and possibly allowing real-time release. Continuous gathering of critical process information during production should allow real-time process adjustments to keep product specifications within predefined limits, hence avoiding batch loss. For a long time, innovations in pharmaceutical manufacturing and quality assurance have been slowed down by the stringent regulatory constraints within the pharmaceutical industry which allowed little room for change and which significantly contributed to the aversion to bring new manufacturing technologies and quality assurance methods to the attention of the regulators (in order to avoid delaying regulatory approval). The PAT initiative to move towards a risk- and science based approach for pharmaceutical processing is now strongly encouraged by the most important pharmaceutical regulatory authorities (e.g., FDA and the European Medicines Agency, EMA).

Process analyzers are the essential PAT tools for real-time process monitoring and control as they supply the data from which relevant process and product information and conclusions are to be extracted. Available tools have evolved from those that predominantly take univariate process measurements, such as pH, temperature, and pressure, to those that provide multivariate information related to biological, physical, and chemical attributes of the materials being processed (e.g., Raman and NIR spectrometers). In a PAT environment, real-time process measurements can be

- *at-line*: measurements where the sample is removed, isolated from, and analyzed in close proximity to the process stream.
- *on-line*: measurements where the sample is diverted from the manufacturing process, and may be returned to the process stream.
- *in-line*: measurements (invasive or noninvasive) where the sample is not removed from the process stream [FDA, 2004].

The following aspects should be considered when implementing process analyzers into process streams:

- selection of a suitable process analyzer or combination of complementary process analyzers able to monitor the desired critical process and product information,
- determination of the locations in the process streams where and how process analyzers should be and can be implemented to monitor the required information,
- determination of the optimal measurement conditions for the process analyzer to obtain useful data,
- validation of the performance of process stream analyzers (over time).

Since the last decade, near infrared (NIR) and Raman spectroscopy have been increasingly used for real-time measurements of critical process and product attributes during pharmaceutical processing, as these spectroscopic techniques allow rapid and nondestructive measurements without sample preparations. Furthermore, probes coupled to the spectrometers by fiber optic cables can be implemented directly into the process streams allowing continuous real-time in-process measurements. A quick search in Web of Sciences® shows the strongly increased number of publications during the last decade about the use of Raman and/or NIR for pharmaceutical in-process measurements. Besides the practical advantages, an important reason for the high interest for Raman and NIR spectroscopy as process analyzers is their ability to supply versatile and multivariate information. One single spectrum may contain qualitative and quantitative physical and chemical information.

This paper aims at reviewing the use of Raman and NIR spectroscopy in the PAT setting, i.e. *during* processing, with special emphasis in pharmaceutics and dosage forms. Hence, there will be focused on applications where NIR and Raman spectroscopy have been used in-line, at-line and on-line to monitor and control pharmaceutical production processes in real-time. Many studies have been performed using Raman and/or NIR spectroscopy as off-line tools for chemical and physical analysis of pharmaceuticals (e.g., API quantification in tables, co-crystal screening, etc.). Evidently, these studies also contribute to the increased understanding of the production of pharmaceuticals. Several reviews describe and evaluate these off-line Raman and NIR applications (Aaltonen et al., 2008; Aaltonen et al., 2009; Fevotte, 2007; Heinz et al., 2009; Luypaert et al., 2007; McGoverin et al., 2008; Pinzaru et al., 2004; Radtke et al., 1999; Rasanen and Sandler, 2007; Reich, 2005; Strachan et al., 2007; Tantipolphan et al., 2008; Tummala et al., 2005; Wen, 2007; Yu et al., 2007).

2. **NIR versus Raman spectroscopy**

NIR and Raman spectroscopy are both molecular vibrational spectroscopic techniques studying vibrational transitions in molecules.

2.1. Raman spectroscopy

The Raman effect was first observed in 1928 by Sir C.V. Raman (Raman and Krishnan, 1928). However, this effect was already predicted in 1923 by Smekal, based on theoretical calculations

(Smekal, 1923). The Raman effect is the inelastic scattering of electromagnetic radiation (EMR) as a result of energy exchange between the radiation and molecular vibrations. The theoretical background of the Raman effect is well described in literature (Gardiner, 1989; Long, 1977; Nakamoto, 1986; Stoicheff, 1959).

In Raman spectroscopy, the samples are irradiated with monochromatic laser light. Typically, lasers producing laser light in the visible (e.g. 532 nm) or near-infrared (e.g. 785 nm and 1064 nm) range are used. The energy of this light is higher than the energy needed to bring molecules to a higher vibrational state (Figure 1). Most of the incident radiation is scattered by the sample molecules at the same frequency (= energy). This identical scattered light is called Raleigh radiation. Only 10^{-8} is scattered inelastically by the sample molecules, indicating that energy exchange occurred between the incident light and the sample. This inelastic scattering is called the Raman effect. This inelastic scattered radiation can have a lower energy (lower frequency) than the incident radiation or a higher energy (higher frequency) than the incident radiation. The first type of inelastic scattering is called Stokes radiation, the latter anti-Stokes radiation (Figure 1). At room temperature, mainly Stokes radiation will occur. At high temperatures (e.g., 500°C), many sample molecules are already at a higher vibrational state as can be derived from the Boltzmann distribution, hence favoring anti-Stokes radiation.

The selection rule for molecules to be Raman active is that a *change in polarizability* of the molecule occurs during its normal modes. The *polarizability* of a molecule is the ease with which the electron cloud of a molecule can be distorted after bringing the molecule in an electromagnetic field (i.e., by light irradiation). However, molecules are no static entities, but continuously in motion by vibrations, rotations and translations. The actual vibration of a molecule seems arbitrary, but is in fact the superposition of some simple vibration modes, called normal modes. Each of these normal modes has its own frequency. An atom has 3 degrees of freedom (x, y and z direction). Hence, a molecule containing N atoms has 3N degrees of freedom: 3 translations, 3 rotations (2 for a linear molecule) and 3N-6 normal modes (3N-5 for linear molecules). For a diatomic molecule, e.g., the ease to distort the electron cloud will be different for the three vibration states of its harmonic vibration having frequency ν_v, as schematically shown in figure 2a. The larger the bond distance, the further the electrons are apart from the nuclei an thus the easier they can be moved. This change in ease with which the electron cloud of a molecule can be distorted (i.e.; change in polarizability) is needed for Raman activity. Complicated quantum mechanics and the group theory are needed to determine for which of the normal modes of complex molecules a change in polarizability occurs.

A Raman spectrum displays the frequency difference between the incident radiation and the scattered radiation, expressed as wavenumbers, versus the intensity (I) of the scattered radiation (Figure 3). Placzek developed the following equation which allows the calculation of the Raman intensity during a particular vibration:

$$I = cte\left(\frac{\nu_0 + \nu_v}{\nu_v}\right)^4 \frac{NI_0}{1-e^{(-h\nu_v/kT)}}\left[45\left(\alpha^S\right)^2 + 13\left(\alpha^a\right)^2\right] \qquad [1]$$

where: v_0 is the frequency of the incident radiation

v_v is the vibration frequency of the molecule

N is the number of irradiated Raman active molecules

I_0 is the power of the light source

h is Planck's constant (= $6.6260.10^{-34}$ Js)

k is the Boltzman's constant

T is the temperature

α^S is the polarizability from the molecules causing Stokes radiation

α^a is the polarizability from the molecules causing anti-Stokes radiation.

However, besides these parameters the Raman intensity is also determined by instrumental (e.g., detector, length of glass fiber when using probes, etc.) and sample parameters (e.g., sampling volume, sample particle size, refractive index of sample, concentration of the considered compound, etc.). Furthermore, as scattering occurs in all directions, only a fraction is detected. When probes are implemented into process streams, only the light which is scattered into the same direction as where the incident light comes from is measured.

The irradiation of materials can result in different phenomena: scattering, absorption and fluorescence. As the Raman effect is inherently weak, the other phenomena can interfere strongly. Moreover, heating, photodecomposition and laser ablation can occur. The incident laser light can be absorbed when the wavelength of this light corresponds with the absorption band in the spectrum of the molecule, resulting in the transition of the molecule to the excited state (dependent of the laser to the excited vibrational or electronic state). The absorbed energy is then transformed via radiationless transitions into thermic energy. This absorption interferes quite strongly with the Raman effect as the intensity of Raman scattering is proportional to the intensity of the laser light. This interference can be avoided by using another wavelength laser. Besides the absorption of the laser light, absorption of the scattered light can likewise occur. Fluorescence can produce substantial interferences in Raman spectroscopy when the molecule is excited to an electronic excited state. The molecule decays to a lower energy level by a radiation-less transition (the vibrational ground state in the electronic excited state), followed by the decay to the electronic ground state (Figure 1). During this last decay, fluorescent radiation is emitted, interfering with the Raman signal. Interference by fluorescence can be avoided employing lasers with other (higher) wavelengths to make sure that no excitation to the electronic excited state occurs. As the intensity of the Raman signal is proportional to the intensity from the laser upon the sample, it is favorable to use as high as possible laser intensities. However, destructive effects can occur by high energy supply. Absorption of radiation with insufficient energy transfer to the surroundings results in sample heating (and possibly destruction). Laser ablation is a phenomenon where material is removed from the sample. Several effects occur simultaneously: photodecomposition, thermic expansion and decomposition. Furthermore, a mechanic effect occurs by a mechanic power of the laser radiation on the sample.

When the energy added to the sample per time unit is larger than the bond energy and when the energy is dissipated, ablation occurs resulting in a crater (Gardiner, 1989; Long, 1977; McCreery, 2000,Nakamoto, 1986; Stoicheff, 1959);

2.2. NIR spectroscopy

The discovery of NIR energy is ascribed to Herschel in the 19th century (Herschel, 1800), but the first industrial applications only appeared in the 1950s. NIR spectroscopy studies the absorption of EMR in the NIR region, i.e. 700 nm - 2500 nm (14300 cm^{-1} – 4000 cm^{-1}). Mid infrared and Far infrared light can be situated in the 2500 nm – 10000 nm and 10 µm – 1000 µm range, respectively. The basic principles of NIR spectroscopy are thoroughly described in a review from Reich, 2005. The detailed theory of NIR spectroscopy can be found in Williams & Norris 1987, Osborne et al 1993, Blanco et al 1998, Chalmers & Griffiths 2002 and Ciurczak & Drennen 2002.

In NIR spectroscopy, the samples are irradiated with NIR light. Some of this NIR light is absorbed by the molecules, bringing them to a higher vibrational state (Figure 1). Common incandescent or quartz halogen light bulbs are most often used as broadband sources of NIR radiation for analytical applications. Light-emitting diodes (LEDs) are also used and offer greater lifetime and spectral stability and reduced power requirements. Only vibrations resulting in *changes in dipole moment* of a molecule can absorb NIR radiation. A dipole is the product of charge (positive and negative) and distance. Figure 2b shows that there is no change in dipole moment during the stretch vibration of an X_2 molecule. Figure 2c shows that there is a change in dipole moment during the stretch vibration of an XY molecule (Visser, 1980). Two-atomic molecules require a permanent dipole to be IR active, while moreatomic molecules only require a dipole induced by the vibration. R-H groups have the strongest overtones as the dipole moment is high. Also O-H, N-H, C-H, S-H bonds are therefore strong NIR absorbers. H_2 does not absorb NIR radiation as no change in dipole moment occurs during its vibrations. Molecules that absorb NIR energy vibrate in 2 modes: stretching and bending. Stretching is defined as a continuous change in the interatomic distance along the axis of the bond between two atoms. Bending is defined as a change in bond angle. A C-H stretch for example will have a fundamental absorption band near 2960 cm^{-1}. The 1st and 2nd C-H stretch overtone will hence occur near 5920 cm^{-1} and 8880 cm^{-1}, respectively. A C-H combination will occur near 4420 cm^{-1}, which is the sum of a C-H stretch (2960 cm^{-1}) and a C-H bend (1460 cm^{-1}). Figure 4 shows an example of an NIR spectrum.

Figure 2a shows 3 possible vibration states of a diatomic molecule. The potential energy of these vibrations is dependent on the bond length as can be seen in figure 5, representing an anharmonic vibration model. At equilibrium, the potential energy is low. Bringing the atoms closer to each other induces repulsion, resulting in an increase in potential energy. Pulling the atoms away from each other in first instance leads to attraction, resulting in an increased potential energy. However, bringing the atoms far enough from each other does not result in further increase of potential energy. Further displacement of the atoms will result in dissociation. However, from the quantum theory, only some vibrational energy levels are allowed, respresented by the horizontal lines in figure 5. These energy levels are not equidistant in an anharmonic model. An NIR spectrum contains overtones and combinations derived from fundamentals which appear in the IR region.

The low molar absorptivity of absorption bands in the NIR region permits the operation in the reflection mode. Hence, spectra can be recorded with minimal or no sample preparations. In the reflection mode, the light reflected by the sample surface (i.e., the non-absorbed light) is measured (Räsänen et al., 2007).

2.3. Raman and NIR spectroscopy

Raman and NIR spectroscopic measurements can both be done in a very fast (seconds) and non-destructive way, making both tools suited for real-time process monitoring. Custom made fiber optic probes connected to the spectrometers can be implemented into process streams. Referring to the different selection rules for Raman and NIR activity (change in polarizability and change in dipole moment, respectively), both vibrational techniques can be complementary. Molecules producing good signals in NIR spectra might produce weak signals in Raman spectra and vice versa. Raman and NIR spectra contain qualitative and quantitative information on the chemical composition and the physical properties (e.g., particle surface, particle size and shape distribution) of the measured sample (Ciurczak et al., 1986; Osborne et al., 1993; Pellow-Jarman et al., 1996; Rantanen & Yliruusi, 1998; Wang et al., 2002; Hu et al., 2006).

Raman and NIR spectroscopic monitoring of pharmaceutical processes typically result in a huge amount of spectral data. Chemometric techniques are obvious to explain the variation in the data and to extract useful process information leading to process understanding and process conclusions. Spectral pretreatment before chemometric analysis is often desired to reduce the effect of interfering variance in which one is not interested, thereby increasing the part of the variance due to parameters of interest (Luypaert et al., 2004). Adequate spectral preprocessing is hence very critical for further chemometric data-analysis and data-interpretation (Rinnan, 2009).

3. **In-process monitoring using Raman and NIR spectroscopy**

During the manufacturing process of solid dosage forms, the active pharmaceutical ingredients and excipients are subjected to several consecutive process steps: synthesis, crystallization, milling, blending, granulation, drying, tableting, coating and packing. Evidently, as not only tablets are produced, also other widely applied unit operations will be reviewed (e.g., extrusion-sferonisation, freeze-drying, etc.). Within the scope of increased process efficiency and increased production, there is the intention within the pharmaceutical industry to move from traditional batch processing to continuous processing (Vervaet and Remon, 2005). Continuous production processes are based on the ‘one-in-one-out’ principle, and avoid scale-up issues, reduce cycle times, reduce production costs, ensure faster product release, reduce variability, increase flexibility and efficiency, and improve product quality. It is obvious that the current conventional quality control systems of production processes, based on mainly off-line analyses in analytical laboratories, would annul the advantages of continuous processing, and that continuous real-time quality control is indispensable for continuous production. The desire within the pharmaceutical industry to shift towards continuous processing strengthens the desire and need to invest in PAT. This review mainly focuses on the applicability of Raman and NIR spectroscopy for *in-process* analysis during the production of solid dosage forms. The use of Raman and NIR spectroscopy for the in-process monitoring of drug synthesis processes and crystallization processes is evaluated in Rantanen (2007) and Räsänen and Sandler (2007).

Process analysers are the essential PAT tools for real-time process monitoring and control (in-line, on-line or at-line) as they supply the data from which relevant process and product information and conclusions are to be extracted. The following steps should be applied to implement process analyzers in process streams:

- Determination of all required critical information. In order to determine crucial and relevant information (e.g., process step endpoints, intermediate or end product quality requirements), as much as possible pharmaceutical technological knowledge should be gathered from the available literature and in-house process knowledge. It is essential to know which intermediate process step endpoints have to be reached and which required intermediate quality attributes should be obtained before the next process step can start. The relevant quality parameters should be defined.
- Selection of the suited process analyzer or combination of complementary process analyzers able to supply the required critical information.
- Determination of the locations in the process streams where process analyzers should be and can be implemented.
- Determination of optimal process analyzer measurement conditions to obtain useful data.

Rantanen (2007) clearly described the challenges in process analysis with Raman spectroscopy and discussed several approaches to overcome them (Figure 6). Similar challenges and solutions are observed and valid for in-process NIR spectroscopy.

Table 1 shows an overview of many publications in which the use of Raman and NIR spectroscopy for in-process monitoring of pharmaceutical unit operations has been evaluated. For each of these studies the in-process interfacing of the spectroscopic tool, the monitored information, the discussed challenges and the applied spectral preprocessing and data-analysis methods are specified.

3.1. Blending

Blending is a critical unit operation of the production process of many solid dosage forms. The quality of products depends on the degree of mixing of their constituents, which guarantees the homogeneity of the final product. Mendez et al., 2010 recently proposed a simple and practical operational qualification procedure to investigate the pharmaceutical mixing operation on a large scale. Compared to NIR, the use of Raman spectroscopy for the in-line monitoring of pharmaceutical blending processes has been less described in literature. Vergote et al. (2004) used Raman spectroscopy for the in-line monitoring of the blending process of a binary mixture (50/50, w/w) of diltiazem pellets and paraffinic wax beads (particle size: 800 – 1200 μm). The mixing bowl contained a glass window in front of which a fiber optic non-contact probe was placed. The mean square of differences (MSD) between two consecutive collected spectra was used to identify the endpoint of mixing (i.e., homogeneity). Once homogeneity is obtained, the spectra remain constant resulting in an MSD of zero. Wikström et al. (2005) investigated the importance of the Raman spectrometer sampling optics regarding the assessment of powder mixture homogeneity. They found that large spot non-contact optics (spot size 3 mm instead of 60 μm) provide significant advantages because of the enhanced sampling volume and the greater robustness to fluctuations in sampling distance during processing. Rantanen et al. (2005a) also found that the sample volume seriously affected the performance of calibration models for the quantification of anhydrate/hydrate powder mixtures

using Raman and NIR spectroscopy. The calibrations were significantly improved using larger sampling areas. Furthermore, the authors showed that multivariate regression not always improves the predictability of the data compared to univariate analysis. As mentioned in 2.1., the detection sensitivity of Raman spectroscopy is rather low. Hence, there lays an important challenge in the in-line monitoring of low dose blend uniformity. Hausman et al. (2005) showed the ability of Raman spectroscopy to determine the endpoint of the blending process of a low dose, 1%, azimilide dihydrochloride formulation. However, it should be emphasized that low dose detection is very formulation dependent and strongly depends on the Raman activity of API and excipients. De Beer at al. (2008) presented a Soft Independent Modelling of Class Analogy (SIMCA) model allowing the determination of the homogeneity of blends in-line and real-time using Raman spectroscopy in combination with a fiber optical immersion probe.

As water is a weak Raman scatterer, Raman spectroscopy presents itself as a suitable tool for measurements in aqueous environments. De Beer et al. (2006) showed the ability of Raman spectroscopy to monitor in-line the homogenization process of an aqueous pharmaceutical suspension. At the same, time it was possible to quantify the API concentration in the suspension.

NIR applications assessing powder blend homogeneity are numerous. Hailey et al. (1996) demonstrated the interfacing of NIR with a blender. Complete supervisory control and data analysis (SCADA) software controlled the blender and spectrometer operation and performed statistical spectral data analysis in real-time. Sekulic et al. (1998) studied the effect of different preprocessing approaches (detrending, standard normal variates (SNV), second derivatives, and the combination of detrending and standard normal variates) on NIR spectra collected in-line during powder blending. Depending on the purpose of the application, the user may or may not be interested in the spectral contributions originating from the physical characteristics of the sample. Where these characteristics are important, the user may choose to work with the raw spectral data, otherwise some pre-treatment or preprocessing is usually carried out. Furthermore, the authors evaluated several algorithms used to determine blend homogeneity (mean standard deviation versus blend time, moving block standard deviation, dissimilarity calculations, principal component analysis (PCA) and SIMCA). These blend profiling approaches did not show any appreciable differences in this study. El-Hagrasy et al. (2001) used NIR spectroscopy noninvasively to monitor powder blend homogeneity. They showed that multiple sampling points are needed for accurate and precise estimation of mixing endpoint. Therefore, six sapphire windows were mounted at different locations on the V-blender through which NIR spectra were collected. Shi et al. (2008) showed that the blending behavior at two sensor locations demonstrated a significant difference for endpoint and blending variability. In another study El-Hagrasy et al. (2006a) used a design of experiments approach to identify the critical factors affecting powder blending. The effect of humidity, component concentration and blender speed was evaluated on mixing endpoint, particle size and density of powder. All these variables were shown to have a significant effect on the blending endpoint. Moreover, humidity and concentration had a significant effect on particle size and powder density. NIR spectroscopy showed to be sensitive to changes in physicochemical properties of the mixtures. The authors found that 2nd derivative spectral preprocessing was suitable to minimize the spectral variations due to changes in physical properties, while monitoring chemical changes. In another study, El-Hagrasy et al. (2006b) developed two pattern recognition models (SIMCA and Principal Component Modified Bootstrap Error-adjusted Single-sample Technique, PC-MBEST) combined with 2nd derivative preprocessing on

the spectra, allowing to predict the blend homogeneity of independent blend samples manufactured under different processing conditions (humidity, blender speed, component concentration). Barajas et al. (2007) developed an NIR spectroscopic method for the monitoring of flowing pharmaceutical powders during their voiding and for the detection of post-blending segregation. Particle size differences in powder blends are known as driver for segregation. Zhang et al. (2009) developed a new blending endpoint determination method. A hidden Markov model showed to have a better reliability, a higher robustness and a more transparent endpoint decision making compared to the traditionally MBSD method. Ufret and Morris (2001), used NIR spectroscopy throughout blending runs to obtain the mixing profile and the dynamics of the powder bed as function of the blender rotations. This approach elucidated the existing relationship between the characteristic mixing parameters (e.g., formulation ingredients, geometry of the mixer, batch load) and the required rotations to achieve content uniformity. Bellamy et al. (2008) studied the effects of particle size and cohesive properties on mixing with non-contact NIR. They found that the magnitude of the 2^{nd} overtone NIR measurements is less affected by changes in particle size compared to the 1^{st} overtone. Furthermore, the peak-to-peak noise of the 2^{nd} overtone NIR mixing profile increases with the particle size of the added compound. Li et al. (2007) showed the importance of a large beam size on the real-time determination of powder blend homogeneity by NIR spectroscopy.

Several publications describe the possibility to quantify API and excipients during blending using NIR spectroscopy. El-Hagrasy et al. (2006c) developed several univariate and multivariate quantitative NIR models for prediction of blending endpoint. They found that linear regression, using a single wavelength, yielded optimum calibration and prediction results. Sulub et al. (2009) used a set of 21 off-line static calibration samples for the development of a multivariate partial least squares (PLS) calibration model for in-line prediction of the API content during the blending process. Wu et al. (2009) quantified the constituent concentrations of both drug and excipients in powder blends using NIR spectroscopy. The authors concluded that the measurement uncertainties were higher for minor components in the powder formulations. Karanda et al. (2010) studied the difference between static and dynamic spectral acquisition. They found that dynamic spectral acquisition resulted in the most accurate predictions for all blend components. The authors further emphasize the importance of adopting appropriate and similar sampling strategies for both calibration and actual testing.

El Hagrasy et al. (2006d) reported the use of NIR spectroscopy for monitoring of adequate lubricant (magnesium stearate, 0.5 – 9.0 %) mixing into pharmaceutical granules. Herewith, the significance of sensor location on the blender at different fill levels was evaluated. They found that different mixing endpoints were concluded dependent on the location of the NIR probe.

3.2. Wet granulation

High shear granulation and fluid bed granulation are the two most applied wet granulation techniques for the production process of pharmaceutical solids. During granulation, the powder particles are mixed with a granulation liquid leading to compound particles. Granulation aims at improving the material properties for further processing: improved flow properties, less demixing, better compressibility and less dust production.

NIR and Raman spectroscopy have been mainly applied for the in-line monitoring of water content, particle size distribution, API solid state and endpoint of granulation processes. Furthermore, the

spectroscopic process fingerprints have been used to increase the understanding of the granulation process.

List and Steffens (1996) demonstrated as first the use of NIR spectroscopy for the in-line solvent content determination during granulation. Rantanen et al. (2001a) showed that in-line NIR moisture determination during fluid bed granulation is possible based on the simultaneous detection of only four wavelengths. An entire NIR spectrum is not necessary for water determination, and often the use of only a few NIR wavelengths around the water band enables reliable and high-speed detection of moisture. In another study, Rantanen et al. (2000) evaluated the factors affecting in-line NIR moisture measurements with the above mentioned four-wavelength sensor. They found that particle size effects influence the spectral baseline and that the applied binder influences the NIR measurement. Watano et al. (1996) studied the effects of operational variables on the NIR measurement and found the effect of the granulation liquid flow rate and process air temperature to be significant. Several authors described the simultaneous determination of moisture content and particle size data using NIR spectroscopy. Frake et al. (1997) and Findlay et al. (2005) demonstrated the simultaneous real-time monitoring of particle size and moisture content using NIR through a window into the bed of a fluidized bed granulator. This measurement setup avoids fouling and sticking of the wet material to the measurement device.

Luukkonen et al. (2008) predicted granule and tablet quality properties such as particle size, porosity and hardness using in-line NIR data (i.e., the first NIR overtone band for water at 1460 nm) from a high-shear granulation process. Alcala et al. (2010) acquired NIR spectra through a glass window of a fluidizer during a wet granulation process. PCA of the NIR data allowed to distinguish between the different steps of the granulation process. A PLS model was developed allowing the prediction of moisture content, particle size distribution and bulk density.
Li et al. (2005) used NIR spectroscopy for the quantitative monitoring of polymorph conversion of an active pharmaceutical ingredient during a wet granulation process. Wikström et al. (2005 and 2008) described the feasibility of Raman spectroscopy for in-line monitoring of the transformation of theophylline anhydrous to theophylline monohydrate during high shear wet granulation. Process induced transformations are important to be controlled as they can alter the API properties in the drug product, including therapeutic efficacy. They also found that process settings (e.g. mixing speed) influence the start and rate of transformation.

Rantanen et al. (2001b) visualized a fluid-bed granulation process based on NIR spectroscopic multivariate process data. Self-organizing maps (SOMs) were used to visualize the process consisting of a number of process states. In another study, Rantanen et al. (2001c) showed that in-line NIR measurements provide information related to the amount of water throughout a fluid bed granulation process. This information combined with trend charts of the temperature difference between process inlet air and granules and the water content of process air enabled the control of water during fluid bed granulation and the analysis of the different granulation processes phases. Hence, in-line information on all granulation process steps was obtained. In 2005(b), Rantanen et al. monitored a high shear granulation process using NIR spectroscopy. In combination with PCA methods, three separate phases during the process could be elucidated. Information on the homogeneity of the formulation, the amount of water in the wet mass and the granule particle size was extracted from the NIR data. Hence, NIR allowed to determine the endpoints of the three

subphases of a high shear wet granulation process. Jorgensen et al. (2004a and 2004b) described in two manuscripts the visualization of a small-scale high-shear granulation process using in-line NIR spectroscopy and chemometrics. Physical (impeller torque and temperature) and chemical (NIR spectra) information were continuously monitored during granulation. Process vectors were created combining all data and describing all relevant information. The visualization of the vectors was done using PCA and SOM. None of the individual measurement techniques were able to describe the state of the process alone.

Tok et al. (2008) analyzed and compared the responses of NIR, focused beam reflectance measurements (FBRM) and acoustic emission measurements to monitor a pilot-scale fluidized bed granulation process. All three process analyzers were able to detect the three granulation phases (wetting and nucleation, consolidation and growth, breakage) to varying degrees of sensitivity. FBRM and NIR were susceptible to fouling on probe windows. Walker et al. (2007 and 2009) proposed a novel use of Raman spectroscopy, which allows in situ measurement of the composition of the material within the fluidized bed in three spatial dimensions and as function of time. This was achieved by recording Raman spectra from specific volumes of space using a probe positioned within the fluidized bed on a long-travel x-y-z stage, hence providing 3D maps of the concentration and the chemical structure of the particles in motion in a fluidized bed within 10 seconds.

3.3. Drying

In 2000, Morris et al. presented a method to accelerate the fluid bed drying process relying on concepts of heat and mass transfer with real-time NIR monitoring of moisture. Critical NIR readings were used corresponding to the end of the evaporative cooling as temperature-independent endpoint. Räsänen et al. (2003) studied the dehydration behavior of theophylline granules using a novel multichamber microscale fluid bed dryer with a process air control unit and in-line NIR spectroscopy. The stepwise dehydration of materials was followed by the water content difference of inlet and outlet air temperature, the pressure difference over the bed, and in-line NIR spectroscopy. Green et al. (2005) examined different sampling configurations to improve the accuracy of the in-line residual moisture content determination during a fluid bed drying process. In-line NIR data were collected (i) using the probe directly inserted into the fluid bed dryer such that measurements of dynamic flowing sample were collected, and (ii) using the NIR probe interfaced to a home-made sheath allowing static sample collection and utilizing an air purge to clean the probe face, thereby preventing probe fouling. This latter device was (iii) further modified to allow thieving of the actual sample being measured. They found that the latter sampling device allows collection of quality spectra in process systems and eases method development as NIR and reference measurements are performed on the same samples. Nieuwmeyer et al. (2007) demonstrated that NIR spectroscopy could be used for simultaneous water content determination (with errors comparable to the reference method) and median granule size. Romer et al. (2008a) proved that in-line NIR measurements enable real-time monitoring of API (erythromycin dihydrate) phase transformations. Kogermann et al. (2008) demonstrated the ability of Raman and NIR spectroscopy for in-line quantitative solid state transformation during dehydration. Aaltonen et al. (2007) showed the complementarity of Raman and NIR spectroscopy for the quantitative in-line monitoring of solid-state transitions during fluidization. NIR spectroscopy was particularly sensitive to water while Raman spectroscopy to crystal structure changes. Märk et al. (2010) implemented a continuous NIR

measuring setup to rapidly gain product assay, water content and residual solvent information during the fluid bed drying process in the production plant of an antibiotic substance. A bypass system outside the drier combined with a robust process probe proved to provide the best sampling system geometry. The spectrometer was equipped with an additional laboratory probe for simultaneous offline analysis. The process probe results were in agreement with the laboratory probe results. Hartung et al. (2010) showed that tablet characteristics after compression of granules are not only dependent on the residual moisture content of the granules but also on the moisture profiles during the entire fluid bed granulation process. The authors showed that 2 granule types with the same residual moisture content but with different moisture profiles during the entire fluid bed granulation/drying process are different. Granules with a low-moisture profile and a low residual moisture content have little water adsorbed on the surface of the granules, while for granules with a high-moisture profile and a likewise low residual moisture content the water had time to partially diffuse into the structure of the solid granule particles and to form liquid bridges. Peinado et al. (2010) developed a PLS model, based on NIR spectra and humidity determinations, allowing the in-line prediction of the drying endpoint of a fluidized bed process. The in-process method was validated according to the ICHQ2(r1) guidelines. However, this guideline is not adopted to in-process methods developed and validated only with in-line samples in dynamic systems. Therefore, the authors propose a customized guideline addressing these challenges.

3.4. Tableting

Raman and NIR spectroscopy have been widely used to analyze (API quantification, solid state identification, process induced transformations) pharmaceutical tablets off-line in a fast, direct and non-destructive way as described by Räsänen and Sandler (2007) and Rantanen (2007). Therefore, there is a desire to use Raman and NIR spectroscopy in-line to evaluate tablets. The potential analysis speed of Raman and NIR spectroscopy should make it possible to largely increase the number of analyzed tablets (non-destructively) before release compared to the current situation where traditional off-line analysis methods (e.g. HPLC) are used. However, publications describing the *in-line* use of Raman and/or NIR spectroscopy and tool interfacing for tablet analysis are scarce. Johansson and Folestad (2003) discussed the potential use of Raman spectroscopy for monitoring tableting processes. Aaltonen et al. (2008) thoroughly reviewed to possibilities of using spatially offset Raman spectroscopy for the analysis of tablets. For this Raman spectroscopic analysis method, the Raman scattering is collected from a different sample portion than the irradiated sample fraction. Hence, fluorescence interference can be reduced as there is no emission from the sampled portion. Tabasi et al. (2008a) described the application of NIR spectroscopy to monitor a tablet manufacturing process. NIR spectroscopy in combination with multivariate modeling was used as a rapid and nondestructive technique for the prediction of content uniformity, compression force and crushing strength for orbifloxacin tablets. Cogdill et al. (2004) presented the development and validation of a PAT based NIR method for the on-line prediction of tablet hardness and API content.

3.5. Coating

Kirsch and Drennen (1996) and Andersson et al. (1999) demonstrated the applicability of at-line NIR spectroscopy as an accurate, rapid and non-destructive tool for the determination of the amount of polymer film on tablets. Andersson et al. (2000) provided a first in-line study in which NIR

spectroscopy was used for the quantitative analysis of film coating on pellets in a fluidized bed process. Measurements were done utilizing a diffuse reflectance fiber-optic probe positioned inside a fluidized bed process vessel. The authors thoroughly describe the probe interfacing in the fluid bed. Besides the coating thickness determination with high precision, also an estimate could be obtained of the coating thickness variation. A similar study was done by Perez-Ramos et al. (2005) and Romer et al. (2008b) in a pan coater and rotating plate coating system, respectively. These authors also emphasize that a sufficiently fast sampling rate is needed and that the fiber optic probe or sensor has to be optimized for the monitoring purpose. Lee et al. (2010) proposed new approaches to develop a reasonable dynamic calibration model for the in-line monitoring of film thickness of pharmaceutical tablets processed in a fluid-bed coater. Tabasi et al. (2008 b and c) published two papers in which the applicability of NIR spectroscopy for the in-line monitoring of a coating process and its subsequent curing process of a pharmaceutical sustained release product has been proven. Besides coating thickness, NIR spectroscopy is able to detect polymorphic changes during coating processes (Kamada et al., 2009). Raman spectroscopy has also been proved as an adequate tool for coating evaluation. Romero-Torres et al. (2005) suggested the feasibility of Raman spectrometry to examine the variability of tablet coatings. A Raman probe was used that can operate with a revolving laser focus to average content and coating non-uniformity. Furthermore, the authors describe adequate preprocessing techniques that emphasize spectral changes while minimizing the effects of background light scattering and fluorescence. In another study, the same authors used Raman spectroscopy to quantify tablet coating thickness in the presence of a fluorescent ingredient in the coating formulation (Romero-Torres et al., 2006). In a very recent study, Muller et al. (2010) used Raman spectroscopy for the in-line monitoring of an active coating process. Active coating is a film coating process where the API is included in the coating layer. Raman spectroscopy was able to show in-line when the API quantity in the coating was as desired, hence suggesting the endpoint of the pan coating process. To protect the probe against dust, compressed air was blown through an iron pipe, which was attached in front of the probe.

3.6. Pelletization

The number of publications describing the use of Raman and NIR spectroscopy for the in-process analysis of pelletization processes is low. Sandler et al. (2005) used Raman and NIR spectroscopy at-line to increase the understanding of the solid-state behavior of theophylline and nitrofurantoin formulations during pelletization. NIR gave valuable information on the water behavior during processing, but did not allow to detect the hydrate formation in the formulations because of the saturation of the water signal. However, Raman spectroscopy was able to see the hydration and dehydration phenomena during the process proving the complementarity of Raman and NIR spectroscopy. In another study, at-line NIR spectroscopy was applied to understand the process induced transformations of erythromycin dehydrate during pellet production (Römer et al., 2007).

3.7. Freeze-drying

Romero-Torres et al. (2007) and De Beer et al. (2007) described the use of Raman spectroscopy for the fast, non-invasive in-line monitoring of a simple mannitol solution freeze-drying process. Furthermore, De Beer et al. (2009a and 2009b) compared the simultaneous use of Raman and NIR spectroscopy for the in-line monitoring of lyophilization processes. Raman spectroscopy proved to be

an excellent tool for crystallization and polymorphic transformation monitoring during the complete freeze-drying process. As water and ice produce weak signals in Raman spectra, Raman spectroscopy provides clear product solid state information during the freezing phase, primary drying phase and secondary drying phase. In contrast, NIR spectroscopy is suited for the in-line monitoring of the water and ice behavior during freeze-drying. As ice produces huge signals in NIR spectra, NIR spectroscopy is unable to provide detailed solid state information during the freezing and primary drying phase. Brülls et al. (2003) showed as first the use of NIR spectroscopy for the in-line monitoring of a freeze-drying. However, measurements were done invasively in this study. The main disadvantages of Raman and NIR spectroscopy for in-process freeze-drying monitoring is that only 1 vial can be monitored in the current set-up. Both process analyzers showed to be interesting R&D tools for lab-scale freeze-dryers, but the applicability in large production scale freeze-dryers is still far away. In an another study, de Waard et al. (2010) showed the applicability of in-line Raman spectroscopy for controlled crystallization of the lipophilic drug fenofibrate during freeze-drying. Off-line studies suggest that Raman and NIR spectroscopy will be able to monitor in-line secondary protein structure changes during lyophilization.

3.8. Continuous production

Nowadays, there is a major interest within the pharmaceutical industry to move from traditional batch processes towards continuous processes. Several production machine suppliers recently proposed their first versions of continuous production lines: e.g. the ConsiGma™ system from GEA, the EASY FLOW® system from Böhle. The challenge now is the find out if the critical process aspects from the traditional batch processes above can be monitored and controlled in-line in their corresponding continuous production processes. We did not find publications describing the in-line use of Raman and NIR spectroscopy for the in-line monitoring of continuous blending, continuous granulation, continuous drying and continuous coating processes.

Saerens et al. (2010) recently showed the Raman spectroscopic in-line monitoring of a (continuous) pharmaceutical hot-melt extrusion process. Raman spectroscopy allowed the in-line API quantification as well as the polymer and API solid state characterization during processing. Solid solutions showed Raman band broadening compared to solid dispersions. Furthermore, Raman peak shifts appeared in the spectra of solid dispersions and solid solutions compared to the physical mixtures, suggesting interactions (hydrogen bonds) between polymer and API.

4. Conclusions

Raman and NIR spectroscopy have been widely used for the in-process monitoring of several batch unit operations during the production of pharmaceutical solid dosage forms. Both PAT tools are complementary and able to supply physical and chemical critical product and process information during processing, herewith increasing the process understanding. Special attention should be paid to the interfacing of probes into process streams (Figure 6). A next step within the PAT framework, is the use the real-time obtained critical process and product information from the process analyzers, based on feed-forward and feed-back loops, and steer and guide processes towards their desired state. Finally, Raman and NIR spectroscopy will certainly play a key role in the real-time monitoring and control of continuous pharmaceutical production processes, which is currently of major interest within the pharmaceutical industry.

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Table 1: Applications of Raman and/or NIR spectroscopy for the in-process monitoring of pharmaceutical production processes. Some boxes in the table are left open as specified information was not given by the reference. The table is subdivided per described process. Within each subdivision the examples are ordered by year of publication.

Application + formulation	Raman/NIR	In-process interfacing	Monitored critical process information	Evaluated challenges	Data-analyis method	Spectral preprocessing method	reference
1. <u>Blending</u>							
In-line monitoring of powder blending	NIR	Invasive	Homogeneity	real-time control	MBSD	SNV and detrending transformation	Hailey et al., 1996
In-line monitoring of powder blending	NIR	Invasive	Homogeneity	1. Spectral preprocessing evaluation 2. evaluation of different algorithms for blending endpoint detection	MBSD Dissimilarity calculations Principal component analysis	Detrending SNV Second derivatives Combined detrending and SNV	Sekulic et al., 1998
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Multiple sampling points in the blender	MBSD variant	SNV MSC 2^{nd} derivatives	El-Hagrasy et al., 2001
In-line endpoint detection of the blending of a binary pellet mixture	Raman	Non-contact probe in front of glass window in mixing bowl	Blend homogeneity		MSD	Baseline correction Vector normalization	Vergote et al., 2004
In-line homogeneity detection	Raman	Non-contact probe	Blend homogeneity	Raman sampling optics	PCA	SNV	Wikström et al., 2005
In-line monitoring of low dose blend uniformity	Raman	an immersion probe was inserted into the V-blender through the I-bar port	Blend homogeneity	API present in low dose (1%)	1. univariate: peak intensity vs. blend time 2. Mahalanobis distance method	SNV	Hausman et al., 2005
In-line monitoring a an aqueous suspension homogenization process	Raman	Invasive measurement via an immersion probe	1. homogeneity 2. API quantification	aqueous environment	1. conformity index 2. PCR	Pearson's baseline correction	De Beer et al., 2006
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Evaluation of chemical and physical blend properties in NIR spectra	MBSD variant	SNV MSC 2^{nd} derivatives	El-Hagrasy et al., 2006a
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Prediction of blend homogeneity of independent blend samples manufactured under different processing conditions	SIMCA PC-MBEST	2^{nd} derivatives	El-Hagrasy et al., 2006b
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity and API content	Evaluation of univariate and multivariate quantification mehtods	1. PCR 2. PLS 3. MLR 4. Univariate	2^{nd} derivatives	El-Hagrasy et al., 2006c

					calibration		
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Homogeneous mixing of lubricants into granules	PLS	SNV + 2nd derivatives	El-Hagrasy et al., 2006d
In-line monitoring of post-blending	NIR	Invasive	segregation	In-line monitoring of segregation after blending and during voiding		Spectral subtraction	Barajas et al., 2007
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Effect of beam size	PLS	Savitzky-Golay 1st derivatives	Li et al., 2007
In-line endpoint detection of the blending of a multicomponent powder mixture	Raman	Invasive monitoring via an immersion probe	Blend homogeneity		SIMCA	Offset correction and normalization	De Beer et al., 2008
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Effect of particle size			Bellamy et al., 2008
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Multiple sampling points in the blender	PLS + root mean square from nominal value	Savitzky-Golay smoothing and 2nd derivative	Shi et al., 2008
In-line monitoring of powder blending	NIR		Homogeneity	Accurate blending endpoint determination	Hidden Markov model		Zhang et al., 2009
In-line monitoring of powder blending	NIR	Non-invasive	In-line API quantification	In-line quantification method using an off-line external calibration approach	PLS	SNV + 2nd derivative Savitzky-Golay	Sulub et al., 2009
In-line monitoring of powder blending	NIR	Non-invasive	In-line quantifications	In-line quantification of API and excipients simultaneously	PLS PCR MLR	Savitzky-Golay 1st derivatives	Wu et al., 2009
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Static versus dynamic sampling	PLS	SNV	Karanda et al., 2010
2. <u>granulation</u>							
In-line monitoring of fluid bed granulation	NIR		Moisture content	Evaluation of particle size and binder effect		2nd derivatives	Rantanen et al., 2000
In-line monitoring of fluid bed granulation	NIR		Moisture content	Moisture determination based on four wavelengths	ANN		Rantanen et al., 2001a
In-line monitoring of fluid bed granulation	NIR + other non-spectroscopic data	invasive	Visualization of fluid-bed granulation		SOM		Rantanen et al., 2001b
In-line monitoring of fluid bed	NIR + other	Invasive	Moisture		Design of	Baseline correction +	Rantanen et al., 2001c

granulation	non-spectroscopic data		determination		experiments	normalization	
In-line monitoring of high shear granulation	NIR + non-spectroscopic process information	At-line through glass vials	Visualization of a wet granulation process	SOM versus PCA	PCA + SOM	2^{nd} derivative spectra with Savitzky-Golay smoothing	Jorgensen et al., 2004a and 2004b
In-line monitoring of high shear granulation	NIR		Quantitative monitoring of API polymorph conversion	Solid state changes during granulation	MLR	1^{st} derivatives 2^{nd} derivatives 4^{th} derivatives	Li et al., 2005
In-line monitoring of fluid bed granulation	NIR	Non-invasive	Moisture + particle size	Granulation endpoint determination	Weighted linear combinations of individual reflectance values		Findlay et al., 2005
In-line monitoring of high shear granulation	Raman/NIR	Invasive measurements using immersion probe just above impeller to reduce the risk of sample adhesion	Monitoring of hydrate formation				Wikström et al., 2005
In-line monitoring of high shear granulation	NIR	through aperture in the plastic cover of the granulator. aperture was covered with glass in order to avoid coating the collection lens and light source with dust. Adhesion of powder to the glass was avoided by rotating the glass during processing.	Endpoint detection of granulation subphases		PCA	SNV	Rantanen et al., 2005b
In-line monitoring of high shear granulation	NIR	invasive	Process fingerprint	Prediction of granule and tablet properties	Univariate, PLS and multiway PLS		Luukkonen et al., 2008
In-line monitoring of fluid bed granulation	NIR + FBRM + physical acoustic	NIR + FBRM → invasive Acoustic → non-invasive	Endpoint detection of granulation subphases	FBRM and NIR susceptible to fouling	univariate		Tok et al., 2008
In-line monitoring of fluid bed granulation	Raman	Raman probe positioned in fluid bed on a long-travel x-y-z stage	3-D mapping during fluid bed granulation	Multi-point data collection at	univariate		Walker et al., 2009
In-line monitoring of fluid bed granulation	NIR	Non-invasive through glass window	Moisture content, particle size distribution and bulk		PLS	SNV 1^{st} derivatives 2^{nd} derivatives	Alcala et al.,2010

			density				
3. drying							
In-line monitoring of fluid bed drying	NIR	Non-invasive through window	Drying endpoint	Accelerated drying based on NIR measurements			Morris et al., 2000
In-line monitoring of fluid bed drying	NIR	Multi-channel NIR spectroscopy + non-spectroscopic data	Water content	Dehydration behavior of materials	Univariate	Normalization	Räsänen et al., 2003
In-line monitoring of fluid bed drying	NIR	invasive	Moisture content	Evaluation of sampling effects on method accuracy	PLS	SNV + Savitzky-Golay 2^{nd} derivatives	Green et al., 2005
In-line monitoring of fluid bed drying	NIR	invasive	Water content + median granule size		PCA PLS	SNV + Savitzky-Golay 1^{st} derivatives	Nieuwmeyer et al., 2007
In-line monitoring of fluid bed drying	NIR and Raman	Non-invasive	API phase transformations during drying	Raman and NIR are complementary	PLS	SNV	Aaltonen et al., 2007
In-line monitoring of fluid bed drying	NIR	Non-invasive	API phase transformations during drying		PCA	Savitzky-Golay first derivative smoothing + SNV	Romer et al., 2008a
In-line monitoring of fluid bed drying	NIR and Raman	Non-invasive	API phase transformations during drying	quantification	PLS	SNV	Kogermann et al., 2008
monitoring of fluid bed drying	NIR	On-line using bypass system	Product assay, water content, residual solvent	On-line versus off-line	univariate	SNV, MSC, 1^{st} and 2^{nd} derivatives, straight line subtraction	Märk et al., 2010
In-line monitoring of fluid bed drying	NIR	Invasive (design makes product movement cleaning the NIR window)	Drying endpoint	Difference between residual moisture and moisture profile during drying			Hartung et al., 2010
In-line monitoring of fluid bed drying	NIR	invasive	Drying endpoint	An adapted ICHQ2(r1) guideline was proposed which is suitable for in-process methods developed and validated only with in-line samples in dynamic systems.	PLS	SNV	Peinado et al., 2010
4. tablet manufacturing							

Monitoring of tablet manufacturing	NIR	Non-invasive	Content uniformity, compression force, crushing strength	Use of rapid content NIR analyzer	PLS	SNV + MSC + Savitzky-Golay 1st derivatives	Tabasi et al., 2008
5. coating							
Monitoring of fluid bed coating	NIR	At-line	Determination of amount of polymer coat applied to tablet cores		PCA	MSC 2nd derivatives	Kirsch and Drennen, 1996
Monitoring of coating (rotating drum)	NIR	At-line	Determination of amount of tablet coating	Estimation of maximum depth in coating material	PCA PLS	MSC	Andersson et al., 1999
In-line monitoring of fluidized bed coating	NIR	Invasive. To secure representative sampling during processing, a sample collector that was emptied by compressed air was used inside the vessel. The sapphire window at the probe tip constituted the interface of the probe to samples in the process vessel.	Quantitative analysis of film coating	General aspects of in-line NIR on solids and multivariate batch calibration are discussed.	PLS	SNV MSC 2nd derivatives	Andersson et al., 2000
In-line monitoring of pan coating	NIR	Non-invasive. To avoid coating droplets from damaging the sensor, the top and sides of the sensor were protected with a plexiglass box with a nitrogen purge	Quantitative analysis of film coating	Real-time endpoint detection of coating process	Univariate	2nd derivatives	Perez-Ramos et al., 2005
Monitoring of pan coating	Raman	At-line	Determination of coat thickness	Tablet-to-tablet coating variability	PLS	SNV MSC 2nd derivatives Savitzky-Golay smoothing	Romero-Torres et al., 2005
Monitoring of pan coating	Raman	At-line	Determination of coat thickness	Presence of strong fluorescent interference	Univariate + multivariate	SNV MSC 2nd derivatives Savitzky-Golay smoothing	Romero-Torres et al., 2006
In-line monitoring of rotating plate coating system	NIR	Non-invasive	Prediction of coating thickness		PLS	SNV + Savitzky-Golay smoothing	Romer et al., 2008
monitoring of pan coating	NIR	At-line	Determination of coat thickness and curing	curing	PCA PLS	SNV + 2nd derivatives	Tabasi et al., 2008a and b

monitoring of coating	NIR	At-line	Determination of polymorphic changes during coating	quantitative	Univariate	2nd derivatives	Kamada et al., 2009
In-line monitoring of fluid bed coating	NIR	invasive	Prediction of film thickness	Dynamic calibration	PCA PLS	MSC	Lee et al., 2010
In-line monitoring of pan coating	Raman	Non-invasive. To protect the probe against dust, compressed air was blown through an iron pipe, which was attached in front of the probe.	Quantitative determination of API in coat + endpoint determination	Active coating process	PLS	SNV	Muller et al., 2010
6. pelletisation							
Monitoring of pelletisation	Raman/NIR	At-line	API solid-state changes	Complementary Raman and NIR	univariate	2nd derivatives	Sandler et al., 2005
Monitoring of pelletisation	NIR	At-line	Process-induced transformations		univariate	2nd derivatives + Savitzky-Golay smoothing	Römer et al., 2007
7. freeze-drying							
In-line monitoring of lyophilisation	Raman	Non-contact phat probe through quartz window in freeze-drier door	Mannitol phase behavior during freeze-drying		PCA		Romero-Torres et al., 2007
In-line monitoring of lyophilisation	Raman/NIR	Non-contact probes built in the freeze-drier chamber	Product monitoring and process phase endpoint determination	Raman versus NIR	PCA	Pearson's baseline correction	De Beer et al., 2007 De Beer et al., 2009a De Beer et al., 2009b
In-line monitoring of lyophilisation	Raman	Non-contact probe built in the freeze-drier chamber	In-line product behavior monitoring	Controlled crystallization of product	PCA	Pearson's baseline correction	de Waard et al., 2010
8. hot-melt extrusion							
In-line monitoring of hot-melt extrusion	Raman	Contact probe built in the die	In-line product behavior monitoring	API quantification + polymer/drug interactions	PCA PLS	Savitzky-Golay and SNV	Saerens et al., 2010

912

Abbreviations:

- ANN artificial neural networks
- API active pharmaceutical ingredient
- MBSD moving block standard deviation
- MLR multiple linear regression
- MSC multiplicative scatter correction
- MSD mean square of differences
- NIR near infrared
- PCA principal component analysis
- PC-MBEST Technique Principal Component Modified Bootstrap Error-adjusted Single-sample
- PCR principal component regression
- PLS partial least squares
- SIMCA Soft Independent Modelling of Class Analogy
- SNV standard normal variate
- SOM self-organizing maps

Figures

Figure 1: IR and NIR absorption, the Raman effect and fluorescence.

Figure 2a: Vibration states of diatomic molecule

Figure 2b: no change in dipole moment during the stretch vibration of an X_2 molecule

Figure 2c: change in dipole moment during the stretch vibration of an XY molecule

Figure 3: Example of a Raman spectrum (CCl_4)

Figure 4: Example of NIR spectra

Figure 5: Anharmonic vibration model

Figure 6: Factors affecting the interfacing of Raman and NIR spectroscopy into process streams Reprinted with permission from Rantanen, 2007, J. Pharm. and Pharmacol. 59, 171-177. Copyright 2007, Pharmaceutical Press.