JPP Journal of Pharmacy and Pharmacology

JPP 2007, 59: 147–159

Received March 16, 2006
Accepted June 6, 2006
DOI 10.1211/jpp.59.2.0002
ISSN 0022-3573

Near infrared spectroscopy in the development of solid dosage forms

Eetu Räsänen and Niklas Sandler

Abstract

The use of near infrared (NIR) spectroscopy has rapidly grown partly due to demands of process analytical applications in the pharmaceutical industry. Furthermore, newest regulatory guidelines have advanced the increase of the use of NIR technologies. The non-destructive and non-invasive nature of measurements makes NIR a powerful tool in characterization of pharmaceutical solids. These benefits among others often make NIR advantageous over traditional analytical methods. However, in addition to NIR, a wide variety of other tools are naturally also available for analysis in pharmaceutical development and manufacturing, and those can often be more suitable for a given application. The versatility and rapidness of NIR will ensure its contribution to increased process understanding, better process control and improved quality of drug products. This review concentrates on the use of NIR spectroscopy from a process research perspective and highlights recent applications in the field.

Introduction

In a wide range of areas in the pharmaceutical field from drug discovery to product development and manufacturing the use of near infrared spectroscopy (NIR) has been found to be advantageous. Focus on NIR has grown quickly partly due to a demand of process analytical applications in the pharmaceutical industry. Moreover, newest regulatory guidelines have underpinned the increase of the use of NIR technologies. The most powerful advantage of NIR spectroscopy over traditional analytical methods is that the measurements are non-destructive, non-invasive and solid samples do not need pre-treatment. However, one has to bear in mind that, in addition to NIR, a wide variety of other tools are also available for sophisticated analysis in pharmaceutical development and manufacturing, and those are sometimes more suitable for a given application. The use of and comparisons between different spectroscopic tools for solid-state characterization have been reviewed by Bugay et al (2001). The versatility and rapidness of NIR will ensure its contribution to increased process understanding, better process control and improved quality of drug products. This review concentrates on the use of NIR spectroscopy from a process research perspective. The applications of NIR imaging will not be covered and readers are referred to reviews by Clarke (2004) and Tran (2005).

The speed of analysis and flexible sampling decrease the risk of errors due to the lack of weighing and dilution operations (Osborne et al 1993; Han & Faulkner1996). The fast and non-destructive nature of the NIR technique has led to numerous applications in several industries (Williams & Norris 1987; Osborne et al 1993; Workman 1993, 1999; Blanco et al 1998). There have been a number of NIR applications in the food (Osborne et al 1993; Reeves & Zapf 1999), forest (Schimleck et al 2004), textile (Cleve et al 2000), biomedical (Sowa et al 1999; Sasic & Ozaki 2001), petroleum (Parisi et al 1990) and chemical industries (Armenta et al 2005). Later, the pharmaceutical industry has become one of the main application areas for NIR spectroscopy. In pharmaceutics, NIR spectroscopy has been utilized in e.g. the determination of degradation products (Drennen & Lodder 1990) and an active pharmaceutical ingredient (API) of tablets (Gottfries et al 1993; Dreassi et al 1996; Han & Faulkner 1996; Dyrby et al 2002; Laasonen et al 2003), the determination of polymorphic changes of API or excipient (Aldridge et al 1996; Buckton et al 1998; Räsänen et al 2001; Jørgensen et al 2002), the determination of particle size (Ciurczak et al 1986; Frake

Division of Pharmaceutical Technology, Faculty of Pharmacy, University of Helsinki, Finland

Eetu Räsänen

Hospital District of South Karelia, Lappeenranta, Finland

Eetu Räsänen

School of Pharmacy, University of Otago, Dunedin, New Zealand

Niklas Sandler*

Correspondence: N. Sandler, AstraZeneca, Pharmaceutical and Analytical R&D, Material Science Team, B7, Silk Road Business Park, Macclesfield, Cheshire SK10 2NA, UK. E-mail: niklas.sandler@astrazeneca.com

Current address: *AstraZeneca, Pharmaceutical and Analytical R&D, Material Science Team, B7, Silk Road Business Park, Macclesfield, Cheshire SK10 2NA, UK.

et al 1998; O'Neil et al 1998, 1999; Rantanen & Yliruusi 1998), and the monitoring of film coating (Kirsch & Drennen 1996; Andersson et al 2000) and blending processes (Hailey et al 1996; Plugge & van der Vlies 1996; Sekulic et al 1996). In the following chapters, after a very brief theoretical section, a closer look is taken at the use of NIR approaches specifically in recent pharmaceutical process analytical applications.

Theory and characteristics of NIR spectroscopy

A recent review by Reich (2005) thoroughly described the basic principles of NIR spectroscopy. Detailed theory of NIR spectroscopy is also described in several books and review articles (Williams & Norris 1987; Osborne et al 1993, Blanco et al 1998; Chalmers & Griffiths 2002; Ciurczak & Drennen 2002; Pasquini 2003). Therefore, this paper only discusses NIR theory very briefly.

The near infrared region was originally discovered by William Herschel in 1800, when the first non-visible electromagnetic spectra were reported (Herschel 1800). The region lies between the visible and the infrared (IR) region of the electromagnetic spectrum. NIR ranges from approximately 700 nm to 2500 nm, corresponding to a frequency range of 14300 cm^{-1} to 400 cm^{-1} (Osborne et al 1993). Only vibrations that result in rhythmic changes in the dipole moment of a molecule can cause absorbencies in the infrared (Williams & Norris 1987). Absorbance in the NIR region originates from overtones and combinations of fundamental vibrations observed in the mid-infrared region (Osborne et al 1993). The vibration may be described as either stretching or bending (Pimental & McClellan 1960). Most of the absorption bands observed in the NIR originate from stretching vibrations of OH, CH, NH, and SH groups or combinations involving stretching and bending of these groups. The fundamental absorption bands are in the mid IR region. NIR bands are broadly overlapping and weaker than the intensities of the fundamental IR bands. The low molar absorptivity of absorption bands in the NIR region permits the operation in the reflectance mode and hence recording of spectra for solid samples with minimal or no sample pretreatment. When a reflectance mode is utilized with the solid samples, spectroscopy measures the light reflected by the sample surface. Diffuse reflectance contains both chemical and some physical information, which makes the interpretation complicated, but also richer.

In the NIR region absorption bands are weaker than in the IR region, which is one of the key advantages of the technique. Sample preparation is not necessary and spectra can be measured directly from solid materials. For example, glass is relatively transparent for NIR radiation and the spectroscopy can be applied in reflectance mode enabling non-invasive measurements. When off-line analyses are adequate, the samples can even be placed in simple glass vials (Wargo & Drennen 1996; Frake et al 1998).

The NIR signal depends on both the chemical composition and the physical properties of the sample. Numerous factors, such as texture of the particle surface, the particle size and shape distributions, temperature and density of the sample, have an effect on light and thereby effect on NIR measurement (Williams & Norris 1987). However, sometimes these phenomena can be considered as an advantage of NIR spectroscopy because they can be used to gather physical information (Ilari et al 1988; Dreassi et al 1995; Morisseau & Rhodes 1997; Frake et al 1998; O'Neil et al 1998; Kirsch & Drennen 1999). For instance, when particle size increases, the scattering of the light diminishes and the light penetrates deeper into the material, which means that the apparent absorbance increases (Osborne et al 1993). Norris & Williams (1983) found that the normalization of spectral data effectively removed the particle size effect. Thereafter, various procedures have been suggested for modelling the particle size data from the NIR data (Ciurczak et al 1986; Ilari et al 1988; Frake et al 1998; O'Neil et al 1998, 1999; Rantanen & Yliruusi 1998; Otsuka 2004). Figure 1 exemplifies the effect of particle size of glass beads on the absorbance of NIR spectra.

NIR systems performing thousands of measurements per minute are available. Undoubtedly, the NIR measurements are very fast and also non-destructive, which makes these methods advantageous for real-time process control systems. Using fibre optic probes measurements can be done with more flexibility than with traditional methods. NIR spectroscopy can be applied to the packaging line and provides the possibility to perform product identity checks at full line speed (Herkert et al 2001). It is well known that NIR spectroscopy can be used for qualitative and quantitative measurement (Osborne et al 1993; Chalmers & Griffiths 2002; Ciurczak & Drennen 2002).

In contrast to IR spectra, untreated NIR spectra exhibit low specificity. The line widths of NIR are broad resulting in overlapping bands and making assignment of the different features of the spectra difficult. The raw spectra do not show clear peaks characteristic to a specific compound and statistical calculations are required (Lowry et al 2000). An attempt can be made to minimize the overlapping, for example by calculating the second derivative of the absorbance, and a

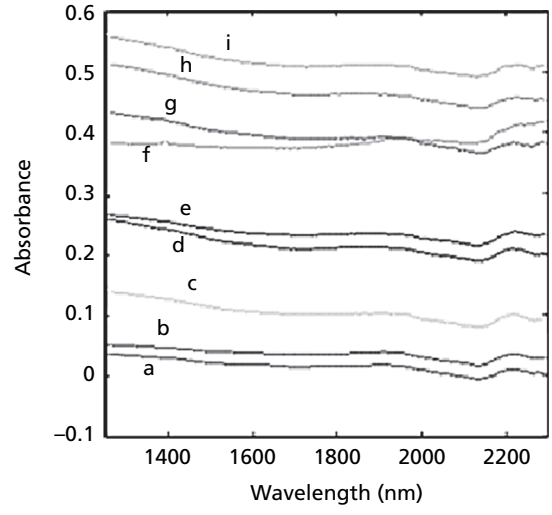

Figure 1 The effect of particle size on the absorbance of NIR spectra using glass beads of different sizes (a–i). a, size range 0.0–0.050 mm; b, 0.0–0.060 mm; c, 0.090–0.135 mm; d, 0.20–0.30 mm; e, 0.200–0.320 mm; f, 0.500–0.750 mm; g, 0.400–0.520 mm; h, 0.650–0.750 mm; i, 1.030–1.230 mm.

more precise analysis of these bands can be made. Specialised chemometrics is often needed to extract the specific information which may sometimes complicate the implementation of NIR spectroscopy. However, with versatile and powerful chemometric techniques, NIR spectra can be related to the values to be modelled successfully, which has been shown in many recent studies (Lopes et al 2004; Stordrange et al 2004; Rantanen et al 2005a). Chemometric issues are discussed in more detail in the next section.

As with other methods, the calibration and validation of NIR methods is critical. It is necessary to analyse representative samples by a time consuming reference analysis method, e.g. HPLC or Karl Fisher titration. Also, calibrations may need to be updated when suppliers change, or when the process is modified (Candolfi & Massart 2000; Wang et al 1998).

Despite these limitations, NIR spectroscopy has become very popular in the pharmaceutical industry because of its many practical advantages. NIR spectroscopy can be seen as a promising technique with several benefits: productivity improvements, cost reduction, real-time monitoring, improvements in quality control, and health and safety of the patients and employees.

Multivariate analysis and NIR

In the field of pharmaceutical technology, the number of different formulations and unit operations creates a problematic field with respect to data analysis (Rowe & Roberts 1998). The analysis of process data is difficult with traditional statistical tools. The process with varying conditions and sequential phases (e.g. fluid bed granulation) cannot be adequately described with, for example, a mean or a smallest and a largest data value. These statistical parameters only give a limited view of the process. Therefore, a multivariate approach is often applied in process analytics. For example, the development of quantitative or qualitative NIR applications most often requires application of multivariate models (Martens & Næs 1989; Lavine 1998, 2000). The term chemometrics is often used to describe an approach to extract chemically relevant information from data produced in chemical experiments (Wold 1995). Commonly used commercial software is usually based on the use of chemometric methods e.g. multivariate linear regression or methods applying principal components. Although there has been a vast increase in utilization of multivariate analysis, there are remaining challenges in the use of these chemometric approaches. One main focus should be put on the deeper understanding of the methodology and principles of multivariate applications.

Quantitative NIR calibrations can be complicated and it is often necessary to use more than two wavelengths due to overlapping peaks and baseline deviations. In many cases hundreds of wavelengths are used most often by employing principal component regression (PCR) and partial least squares (PLS) regression (Fearn 2005). Fearn (2005) discusses the use of the above mentioned regression approaches and states that these have become standard approaches most likely because of their ease of use for less experienced users. Also the availability of excellent software is responsible for the popularity of these techniques. Chalus et al (2005) recently used NIR to determine the active substance content of low dose tablets containing bromazepam and clonazepam. The influence of various spectral pretreatments (standard normal variate (SNV), multiplicative scatter correction (MSC), second derivative (D2), orthogonal signal correction (OSC), separately and combined) and regression methods on prediction error were compared. According to the results, PLS regression provided better prediction than principal component regression (PCR). The PLS models yielded standard errors of prediction (SEP) of 0.1768 and 0.0682 mg for the two products.

The key steps in calibration are the choice of a high-quality set of training samples and validation of results. This simply means that the training set has to be representative, cover the range that it is intended to, and that the calibration is validated with samples of the full variety of all kinds of variability. Cross-validation or separate validation sample sets can be considered, but the choice has to be justified by the application in question. In a recent example by Blanco & Alcalá (2006) it has been shown that the compaction pressure had a marked influence on the spectrum for a tablet and was the primary source of variability among samples. They developed two NIR methods for the analysis of intact tablets by using a calibration set consisting of the spectra for laboratory powder samples and laboratory tablets. It was observed that the model obtained from laboratory compacted tablets was less complex and exhibited a better predictive ability.

An important issue in the use of NIR is the possibility to use calibrations generated on one instrument for predictions on another instrument. However, this can be difficult. Feudale et al (2002) have given an overview of different methods used for calibration transfer and a critical assessment of their validity and applicability. They also give a comprehensive list of references concerning transfer of multivariate calibration models. Leion et al (2005) evaluated a number of methods for transferring quantitative calibrations of NIR diffuse-reflectance data between different instruments. The results indicated that it was possible to transfer calibrations between different instruments, provided that a structured procedure was used.

Process analytical considerations and regulatory aspects

A few years ago the pharmaceutical industry was encouraged to start implementing new technologies in the manufacture of drug products by the introduction of the Process Analytical Technology (PAT) initiative. PAT includes the optimal application of process analytical chemistry (PAC) tools, feedback process-control strategies, information management tools, and product-process optimization strategies to the manufacture of pharmaceuticals (FDA 2004a). Advantages of implementing PAT would be reduced cycle times, prevention of rejects, reduction of human errors by automation, and facilitation of continuous processing to improve efficiency. Another gain of applying PAT would be that laborious testing of the finished product would be avoided because the product could be released based on the in-process documentation. The benefits of implementation of PAT would vary depending on the product. Balboni (2003) has discussed the concepts and principles of PAT. Amongst all measurement technologies it seems that, due to its versatility, NIR will play a most

prominent role in the PAT context. Reich (2005) and Cogdill & Drennen (2005) have recently pointed out practical regulatory aspects dealing with application of NIR spectroscopy. General monographs on NIR spectroscopy have been accepted to the European Pharmacopoeia (Ph. Eur. 2001) and to the United States Pharmacopeia (USP 2003). Moreover, ICH guidelines Q2A (ICH 1994) and Q2B (ICH 1996) can be used to justify validation of quantitative and qualitative NIR spectroscopic methods. Application of NIR spectroscopy, together with other PAT tools will contribute to the quality-by-design concept for the pharmaceutical industry that aims to improve and make pharmaceutical manufacturing more modern in the spirit of Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century (FDA 2004b). The ICH guidance Q8 also addresses these issues (ICH 2005) and the adoption of this philosophy optimally creates product specifications based on mechanistic understanding of how formulation and process factors impact product performance, and therefore bring new opportunities and approaches for industry and regulators.

Applications of NIR in drug development and manufacturing

Precisely controlled systems provide highly repeatable procedures that are essential to industry, especially to drug product development (Browne & Olsson 1998). Issues of instrumentation, validation and implementation of near-infrared spectroscopy for pharmaceutical applications have been recently described by Ciurczak & Drennen (2002). The border between process analytical chemistry (PAC) and more traditional laboratory analysis is sometimes indistinct. The terms in-line, on-line, at-line, off-line, non-invasive are often used variably in literature. Usual definitions are as follows (Callis et al 1987; Blaser et al 1995; Beebe et al 1998; Hassel & Bowman 1998; Workman et al 1999): in-line, the sample interface is located in the process stream; on-line, automated sampling and sample transfer to an automated analyser; at-line, manual sampling with local transport to analyser located in manufacturing area; off-line, manual sampling with transport to remote or centralized laboratory. Many PAT applications will aim at real-time measurement directly from processes. Thus, the interfacing of the spectrometer in to a moving sample or process stream will be an important issue. Andersson et al (2005) recently studied the effect of sample movement on spectral response during fibre probe diffuse reflectance near-infrared spectrometry sampling. The impact on qualitative and quantitative analysis PCA and PLS regression was evaluated using experimental and theoretical simulations. According to their results the spectra with the smallest residuals after projection onto the models generally resulted from non-moving samples or samples moving only slowly. It was shown that the magnitude of the spectral residuals was directly connected to the effective sample size, which related both to sample speed and to the sample area presented to the probe. Recent work by Green et al (2005) discusses the issues concerning sampling and sample presentation during dynamic process monitoring. They performed fluid-bed dryer experiments at 65-, 300-, and 600-L drying scales using several different sampling configurations to improve in-line NIR measurement accuracy and understanding. The results from the study demonstrated that process heterogeneity plays a key role in determination of prediction accuracy. This is important to take into consideration in all in-line measurements, especially in dealing with solids and slurry systems. Interestingly, they also found that depending on the used sampling configuration, the method with the smallest apparent error is not automatically the most optimal for process monitoring and control.

In the following chapters the recent use of NIR is reviewed in terms of different steps of traditional drug manufacturing of solid dosage forms. Figure 2 illustrates an example path of the development or manufacturing of a solid dosage form. We have divided the use of NIR into the following categories: crystallization, measurement of water and drying, crystallinity and crystal polymorphism, identification and quality control of raw materials, blending, different granulation techniques, tablet coating and tableting/capsulation and the final dosage form.

Crystallization and filtration

Crystallization and filtration of pharmaceutical active ingredients is among the most critical and least understood pharmaceutical manufacturing processes, and specifically demanding for those APIs that exhibit several polymorphic forms. Yu et al (2004) have reviewed application of PAT to crystallization processes. They point out that many process and product failures can be traced to a poor understanding and control of crystallization processes. Their review discusses applications to crystallization processes using several case studies. They demonstrate that a variety of in-situ analytical methods, including NIR combined with chemometric tools for analysis of multivariate process information, provide a basis for future improvements in modelling, simulation, and control of crystallization processes. Columbano et al (2002) showed that gravimetric analysis combined with NIRs provided valuable information on the dynamics of the crystallization of

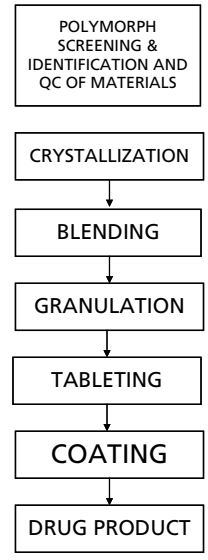

Figure 2 A simplified graph showing the different steps in the manufacturing of solid dosage forms.

salbutamol sulphate. Févotte et al (2004) used fibre optic NIR spectroscopy successfully to investigate and gain deeper understanding of polymorphic transitions during crystallization and filtration of an API. Another pharmaceutical PAC application area of NIR is within the synthesis of pharmaceuticals before the crystallization step. Norris et al (1997) combined NIR with principal component analysis to follow the polymorphic conversion of a crystalline organic compound. Earlier studies showed that NIR could be applied successfully to process monitoring of production of APIs (Norris & Aldridge 1996; Norris et al 1997). Rodrigues et al (2005) described a PAT study on the use of in-situ transreflectance NIRs on an API crystallization. They showed the sensitivity of the technique to changes in process operating conditions and demonstrated its use in both quantitative and qualitative process control.

Measurement of water and drying processes

One of the first pharmaceutical applications of NIR spectroscopy was the measurement of water (Stein & Ambrose 1963; Sinsheimer & Poswalk 1968). The absorption bands of pure water molecules (OH vibrations) occur at 760 nm, 970 nm, 1190 nm, 1450 nm and 1940 nm (Curcio & Petty 1951; Buijs & Choppin 1963, Osborne et al 1993), having increasing absorptivity with increasing wavelength. The most intense absorption bands are located at around 1450 nm (issued from the first overtone OH stretching vibrations) and 1940 nm (caused by a combination of OH stretching and bending vibrations). Figure 3A and B demonstrate the effect of water on NIR spectra with glass beads and theobromine, respectively. The absorption bands are the distributions of vibrations of different OH groups with varying energy levels (Buijs & Choppin 1963; Fornes & Chaussidon 1978; Maeda et al 1995). Using spectral treatment, the individual absorption maxima of each energy level can be distinguished and the NIR measurement can be applied for studying the water–solid interactions within various materials (Iwamoto et al 1987; Delwiche et al 1991; Buckton et al 1998; Luukkonen et al 2001; Räsänen et al 2001; Jørgensen et al 2002).

NIR spectroscopy is useful for detecting hydrates and adsorbed water, since water exhibits strong characteristic absorption bands in the NIR region (Curcio & Petty 1951). With the aid of NIR spectrometry, different energetic states of water molecules in the crystals are seen as absorption maxima in different wavelengths. In addition, hydrate water bands are sharper than other water bands, because the distribution of the OH vibrations is rather uniform, when the water molecules are bound into the crystal lattice. The dependency of the states of water molecules on their hydrogen bonding ability has been established (Luck 1976), and NIR bands shift towards higher wavelength with increasing hydrogen bonding (Buijs & Choppin 1963; Fornes & Chaussidon 1978; Iwamoto et al 1987; Maeda et al 1995). Detection of moisture in freeze-dried solids (Kamat et al 1989; Jones et al 1993; Last & Prebble 1993; Derksen et al 1998), in other solid materials (Plugge & van der Vlies 1993; Dreassi et al 1995; Blanco et al 1997; Harris & Walker 2000) and the on-line moisture determination of microwave vacuum driers (White 1994) has been reported. Recently Zhou et al (2003) determined and differentiated the surface and the bound water in drug substances by NIR spectroscopy. Räsänen et al (2003) studied dehydration of different materials using a multichamber microscale fluid bed dryer with in-line NIR spectroscopy. During controllable fluid bed process conditions, the stepwise dehydration of pharmaceutical solids (e.g. theophylline granules) was established. The batch size in these experiments was only a few grams of studied materials, offering new perspectives (miniaturizing) for pharmaceutical process and formulation studies. Parris et al (2005) very recently described implementation of a miniaturized NIR analyser in a drying process for APIs. The paper also gives perspectives on on-line monitoring technologies and PAT of pharmaceutical processes.

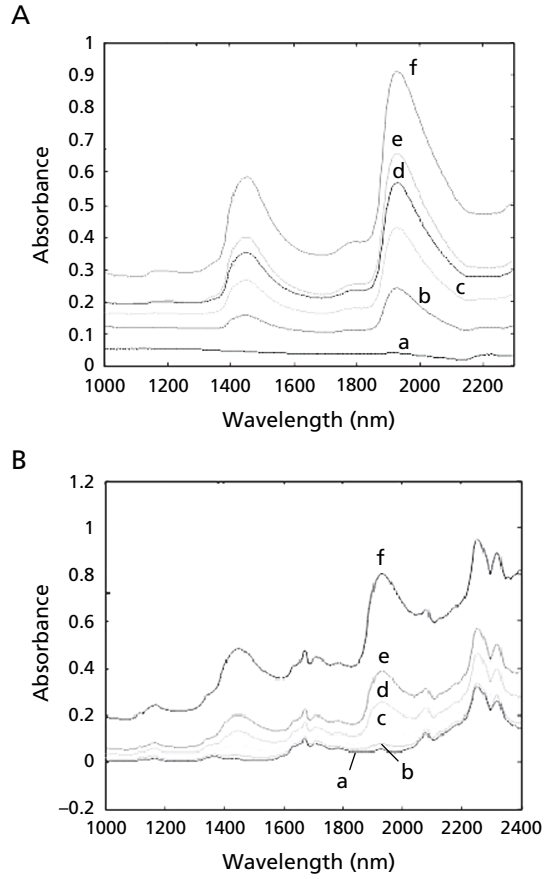

Figure 3 A. Effect of moisture with glass beads a–f. a, moisture content 0%; b, 7%; c, 14%; d, 19%; e, 24%; f, 29% (w/w). B. Effect of moisture content during granulation of theobromine and a granulation liquid with 20% povidone. a, 3%; b, 6%; c, 11%; d, 16%; e, 20%; f, 29% (w/w).

Crystallinity and crystal polymorphism

The dependence of the NIR signal on both the chemical composition and some physical properties of the sample permit not only identification of substances, but also the determination of non-chemical parameters, such as polymorphic forms (Blanco et al 1998). Due to the fact that NIR spectra are sensitive to changes in hydrogen bonding and packing in the crystal lattice, NIR can be applied to analysis of the solid state. It has been used in identification of the desired polymorph

(Aldridge et al 1996), polymorph quantitation (Luner et al 2000; Patel et al 2000; Blanco & Villar 2003) and the determination of crystallinity (Hogan & Buckton 2001).

Seyer et al (2000) investigated the use of NIR spectroscopy for determining degree of crystallinity. Physical mixtures of amorphous/crystalline indometacin and amorphous/crystalline sucrose were prepared over several composition ranges. NIR standard curves demonstrated higher coefficients of determination and lower standard errors than X-ray powder diffraction (XRPD) or differential scanning calorimetry (DSC). Validation standards confirmed the accuracy of NIR over XRPD. Method error analysis demonstrated comparable accuracy for NIR and XRPD, with NIR spectroscopy showing slightly better precision in repeated crystallinity determinations for a 50% crystalline sucrose sample. Further analysis indicated that the NIR differences between crystalline and amorphous sucrose may be attributed to the disruption of regular vibrational modes when crystalline sucrose is rendered amorphous. Gombás et al (2003) reported successful quantitative determination of crystallinity of α-lactose monohydrate by NIR after a spray-drying process.

NIR spectroscopy has also been utilized as a polymorph screening method (Aaltonen et al 2003). Sulfathiazole was recrystallized from various solvents, and the crystals were milled using a planetary ball mill and compressed using a hydraulic press. Polymorphism was then studied by NIR and verified by XRPD and thermal analysis. NIR spectroscopy proved to be a fast tool for polymorph screening and monitoring the processing-induced transformations. They found NIR measurements combined with data clustering by PCA a time-saving improvement for the polymorph analysis in the case of a large number of samples. Blanco et al (2005) examined accelerated transformation of three azithromycin polymorphs (anhydrous, monohydrate and dehydrate) at a high temperature and moisture level by NIR. The limits of detection and quantitation for the dihydrate in monohydrate provided by the NIR method were consistent with those obtained by XRPD. Bai et al (2005) have reported the use of NIR spectroscopy for quantification of glycine crystallinity. A PLS model was developed to correlate the NIR spectral changes with the degree of crystallinity. The results indicated that NIR spectroscopy was well suited to the measurement of glycine crystallinity in lyophilized products. McArdle at al (2005) investigated complementary techniques to probe polymorphism of bicifadine hydrochloride. The study indicated that when analyses were carried out on equivalent sets of spectra, NIR spectroscopy offered significant advantages in quantitative accuracy in determination of polymorphs in the solid state and also proved to be more convenient than ATR-IR and XRPD.

Identification and QC of raw materials

Identification and quality control of raw materials is an everyday analytical problem in the pharmaceutical industry. The publication of the NIR monographs (Ph. Eur., USP) has increased general interest in this method. The USP monograph for instance, describes procedures for testing certain instrument performance parameters including photometric linearity, range, noise, wavelength accuracy, spectral resolution and wavelength repeatability. The issues of sample preparation, mathematical treatment, and the definition of 'identified sample' have been discussed both by the regulatory bodies and by academic groups (Plugge & van der Vlies 1996; Berntsson et al 1998; Blanco et al 1998, 1999; Yoon et al 1998; Moffat et al 2000). In the initial stage of pharmaceutical processes, NIR is used for the identification of raw materials: active substances (Blanco & Romero 2001) and excipients (Candolfi & Massart 2000). The physical properties of the raw material are also determined by NIR spectroscopy, e.g. the particle size of drugs or excipients (Frake et al 1998; O'Neil et al 1998). Cui et al (2004) applied successfully so called temperature-constrained cascade correlation networks (TCCCNs) to the identification of the pharmaceutical powder samples of sulfaguanidine based on NIR diffuse reflectance spectra.

Blending

Determination of homogeneous mixing of the API is important in-process control within the manufacturing of solid dosage forms. The monitoring of blending processes can be performed successfully with NIR (MacDonald & Prebble 1993). Hailey et al (1996) and Sekulic et al (1996) interfaced NIR spectroscopy with blending process equipment used NIR for on-line blend analysis. Sekulic et al (1998) focused on work to investigate qualitative tools of analysis for blend homogeneity determination. Powder blending has also been studied by Ufret & Morris (2001). Skibsted et al (2006) presented two new NIR based methods for mixing; a qualitative and a quantitative method. These were based on the calculation of net analyte signal (NAS) model. The calculations were specific with respect to the API and required no additional reference analysis. The proposed methods were validated by comparing the obtained results with traditional HPLC analysis. The comparisons demonstrated that both the qualitative and the quantitative NIR models showed similar results to HPLC. Li & Worosila (2005) also reported the quantitation of APIs and excipients in powder blends using NIR and multivariate calibration models. El-Hagrasy et al (2006a, b, c) presented an extensive series of studies on powder mixing. In the first study they employed D-optimal design to characterize critical attributes of the blending process and used a NIR fibre-optic probe to monitor mixing through multiple optical ports on the blender. It was found that NIR was sensitive to changes in physicochemical properties of the mixtures, resulting from process variables. The importance of spectral preprocessing was also discussed. In the second study NIR spectral data collected from blending experiments was used to build qualitative models for prediction of blend homogeneity using two pattern recognition algorithms. The third study was an integrated approach for real-time blend uniformity assessment using NIR technology. Various calibration procedures i.e. PCR, PLS and multiple linear regression (MLR) were performed. As a conclusion it was found that linear regression, using a single wavelength, yielded optimum calibration and prediction results. Bodson et al (2006) used NIR successfully in measurements of mixing homogeneity.

Wet granulation

Different granulation techniques, such as fluidized bed or high shear granulation, are often complex unit operations

with several interacting process parameters. No generally accepted real-time in-line tools are offered to gain insight into this process. In practice, it is a necessity to have a highly experienced process formulator and operator to develop a wet granulated solid dosage form. NIR has been widely used in granulation research and in fact the first pharmaceutical process analytical applications of NIR spectroscopy have been the monitoring of complex wet granulation processes (Watano et al 1990; White 1994; Han & Faulkner 1996; List & Steffens 1996; Frake et al 1997; Goebel & Steffens 1998; Rantanen & Yliruusi 1998; Rantanen et al 1998; Morris et al 2000). NIR has frequently been used to monitor the granulation process, for example, to measure the particle size (Rantanen et al 1998), or to follow the moisture content during granulation (Rantanen et al 2000, 2001). The effects of granulation on the structure of cellulose have also been studied (Buckton et al 1999). Recently Otsuka (2006) applied NIR and chemometrics tools to predict the change of pharmaceutical properties of antipyrine granules during granulation by regulation of the added water amount. He concluded that it may be possible that the properties of the granules, such as mean particle size, angle of repose, tablet porosity and tablet hardness could be predicted by a NIR-chemometric method. Li et al (2005) monitored quantitatively polymorph conversion of an API in wet granulation with NIR. The final univariate NIR method was used for off-line or on-line monitoring of polymorph conversion in the wet granulation process.

Airaksinen et al (2003) studied if excipients, α-lactose monohydrate or silicified microcrystalline cellulose could influence the hydrate formation of theophylline in wet masses. They used spectroscopic methods, namely Raman and NIR, to identify hydrate formation in the formulations containing excipients. It was concluded that both methods could identify the hydrate formation even though there were excipients in the formulation. Jørgensen et al (2004a) used NIR to investigate the effect of excipients on the kinetics of hydrate formation in wet masses during granulation. Jørgensen et al (2004b) compared impeller torque measurements and NIR spectroscopy in the characterization of the water addition phase of a high shear granulation process. The results suggested that NIR spectroscopy may be applicable to process monitoring of wet granulation, also in cases where monitoring of impeller torque was difficult to apply. Jørgensen et al (2004c) used physical (impeller torque and temperature) and chemical (NIR spectroscopy) information from a small-scale high-shear granulation to create process vectors. The vectors created were visualized with different methods, namely PCA and the self-organizing map (SOM). The state of the process could not be described by either of the measurement techniques alone, but provided important information about the process. The combining of the data and subsequent data visualizing provided an overview of the process. The authors concluded that the SOM approach had two advantages over the PCA: it presented the results in terms of the original variables and enabled the analysis of nonlinear responses. Both visualization methods could nevertheless be used to describe the progress of the process. Rantanen et al (2005b) investigated the use of in-line NIRs as a process analytical tool for high shear granulation. Critical information, both chemical and physical, was collected during processing, including the homogeneity of the formulation, the amount of water in the wet mass, and particle size information. By efficient data visualization using PCA, NIR spectroscopy could be used to determine the end points of the three subphases of high shear wet granulation, providing a fast in-line quality control tool.

Pelletization

Only a few papers using NIR in pelletization exist. Radtke et al (1999) described studies of moisture content measurement during matrix pellet manufacturing in a rotary fluid bed. Sandler et al (2005) investigated phase transitions occurring in nitrofurantoin and theophylline formulations during pelletization by extrusion-spheronization. An at-line process analytical technology (PAT) approach was used to increase the understanding of the solid-state behaviour of the APIs during pelletization. Raman spectroscopy, NIR spectroscopy, and XRPD were used in the characterization of polymorphic changes during the process. Samples were collected at the end of each processing stage (blending, granulation, extrusion, spheronization, and drying). Water induced a hydrate formation in both model formulations during processing and NIR spectroscopy gave valuable real-time data about the state of water in the system. However, it was not able to detect the hydrate formation in the theophylline and nitrofurantoin formulations during the granulation, extrusion, and spheronization stages because of saturation of the water signal.

Compaction

Roll compaction/dry granulation is an agglomeration process of growing importance. New machine generations and improvements in instrumentation and process control have resulted in an increasing number of pharmaceutical applications of this technique (Kleinebudde 2004). Only a small number of studies exist on the application of NIR to roller compaction of solids. Gupta et al (2005) evaluated the effect of variation in ambient moisture on the compaction behaviour of microcrystalline cellulose powder. They compared the physicomechanical properties and the NIR spectra of compacts prepared by roller compaction and of simulated ribbons (compacts prepared under uni-axial compression). The key sample attributes i.e. relative density, moisture content, tensile strength, and Young modulus, were related to the NIR spectra using multivariate data analysis by PLS. Good agreement was observed between the measured and the NIR-PLS predicted values for all key attributes for the roller compacted samples as well as the simulated ribbons.

Coating of tablets

Monitoring of the film-coating process parameters by NIR has been reported by Kirsch & Drennen (1996). Andersson et al (1999) performed at-line evaluation of the amount of the coating on tablets. Further, Andersson et al (2000) described real-time analysis of film coating of pellets. Roggo et al (2005) describe an application of NIR to detect and identify changes in uncoated and coated tablets in response to pilot-scale changes in process parameters during melt granulation, compression, and coating. NIR is sensitive to changes in coating formulation, the quality of a coating excipient (hypromellose), and coating time. In a concluding quantitative analysis,

they demonstrated the feasibility of NIR in a manufacturing context for predicting coating time and detecting production cores failing to meet dissolution test specifications. In a study by Pérez-Ramos et al (2005) an elegant method was developed to enable in-line analysis of film coating thickness on tablets during a pan-coating operation. Real-time measurements were made using a diffuse-reflectance NIR probe positioned inside the pan during the coating operation to model film growth. It was shown that univariate analysis provided a simple method for in-line monitoring of the coating process using NIR data. An empirical geometric 2-vector volumetric growth model was developed, which explained the coating growth on both face and band regions of biconvex tablets. In-line measurement and use of the created model allowed the coating process to be stopped when a predetermined tablet coating thickness was achieved.

Tableting, encapsulation and the final dosage form

NIR can be applied to perform a final identification test of the active compound in the final dosage form (Dempster et al 1995). The identification of active substances through blister packaging can also be performed e.g. for discriminating between active tablets and placebos during clinical trials (MacDonald & Prebble 1993). However, a large number of publications reflect the advantages of the NIR assay of active substances in semi-finished or finished products such as granules, cores or tablets (Han & Faulkner 1996; Blanco et al 1999). Quantitative measurements for the determination of moisture in finished products are also common applications of NIR spectroscopy (MacDonald & Prebble 1993; Last & Prebble 1993; Roggo et al 2004).

Comparisons of different variable selection methods conducted on NIR transmission measurements on intact tablets have been made (Abrahamsson et al 2003). Reflectance NIR spectroscopy was investigated as a technique to distinguish between the sites of manufacture of a number of proprietary tablets (Yoon et al 2004). Ellis (2005) discussed the applicability of NIR analysis to solid dosage forms. Cogdill et al (2004) presented the development and validation of a PAT-based NIR approach to online prediction of tablet hardness and API content. Blanco & Alcalá (2006) used a NIR spectroscopic method applying PLS regression modelling for the simultaneous determination of the active compounds paracetamol, ascorbic acid, dextromethorphan hydrobromide, caffeine and chlorpheniramine maleate in a pharmaceutical preparation. They validated their method in accordance with the ICH standard and the EMEA validation guidelines for NIR spectroscopy by determining its selectivity, linearity, accuracy, precision and robustness. They concluded that this approach was an effective alternative to existing analytical methods (HPLC and redox titrimetry) used for the same purpose. Alcalá & Blanco (2006) demonstrated a study using NIR in determination of content uniformity and tablet hardness. Feng & Hu (2006) reported universal quantitative NIR models for the analysis of API contents in roxithromycin and erythromycin ethyl succinate tablets from different manufacturers in China. Three different spectrometers were used for model construction to have robust and universal models. They also evaluated the models according to existing ICH guidelines. This study showed that NIR could be a rapid and effective method for non-destructive inspection of medicines in the distribution channels or the open market. Donoso & Ghaly (2005) reported the successful prediction of the disintegration time of tablets using NIR diffuse reflectance spectroscopy. Recently, Bodson et al (2006) reported accurate assays of low-dose riboflavin tablets using NIR and PLS-modelling.

Researchers from the FDA assessed the quality of internet pharmaceutical products using traditional and non-traditional analytical techniques and stated for instance that NIR methods highlighted additional quality issues for the products tested (Westenberger et al 2005). Roggo et al (2005) reported the analysis of tablets having two different origins before and after storage with NIR.

At-line determination of moisture content of gelatine capsules has been performed (Buice et al 1995; Berntsson et al 1997). Berntsson et al (1997) proposed a method in which diffuse reflectance NIR spectroscopy was applied in an at-line process analytical interface to determine moisture content in bulk hard gelatin capsules. Different multivariate calibration methods using MLR and PLS regression and various spectral pretreatments were compared. They concluded that the investigated range for the moisture determination was 5.6–18.0% w/w and the root mean square error of prediction (RMSEP) value was 0.1% w/w. Vredenbregt et al (2006) described a method for fast-screening of sildenafil and counterfeit sildenafil tablets. Their NIR method checked the homogeneity of a batch, distinguished counterfeits and imitations from the authentic product, and detected whether similar samples had been analysed previously.

Cogdill et al (2005a, b, c) presented an excellent series of papers on the use of NIR spectroscopy as process analytical tool for solid dosage forms. They attempted to qualify capabilities of the instrument and the sample handling system, to evaluate the potential effect of one source of a process signature on calibration development, and to compare the utility of reflection and transmission data collection methods. Among other things, they found that the impact of positioning error on both NIR reflection and transmission analysis may be efficiently diminished using spectral preprocessing techniques. Also, they reported that shielding was not required for single-tablet NIR transmission analysis and that diffuse reflection spectra were less sensitive to sample positioning than transmission spectra. Their preliminary research led to NIR investigations on development and validation of quantitative calibrations for API content and tablet hardness. They also reported on method implementation and transfer and addressed theoretical and practical aspects of deploying and maintaining NIR calibrations in a validated PAT application.

Summary

The use of process analytical technologies by the pharmaceutical industry and in pharmaceutical process research is an answer to the growing need for improved productivity and accelerated drug development to meet the increasing competition in this pharmaceutical field. The literature is filled with elegant examples of using NIR in combination with multivariate tools, which can be made use of in characterization of the solid state and drug product manufacture. The latest

developments in the fields of information technology, optoelectronics, data handling and analysis, not to mention general technique improvements, have enabled the instantaneous and non-invasive NIR analysis of pharmaceutical processes operations and given a molecular level approach to processing. The designs and conduct of pharmaceutical development studies should be consistent, underpinning the scientific purpose as it is stated in the ICH guideline Q8. The knowledge gained is important, not the volume of data produced. The use of NIR and appropriate data analysis techniques to support process understanding will play a key role in future drug development, eventually leading to enhanced process understanding for scientific, risk-managed pharmaceutical development, manufacture, and quality assurance in accordance with the PAT ideology and provide a basis to science-based submissions and regulatory evaluation.

References

Aaltonen, J., Rantanen, J., Siiriä, S., Karjalainen, M., Jorgensen, A., Laitinen, N., Savolainen, M., Seitavuopio, P., Louhi-Kultanen, M., Yliruusi, J. (2003) Polymorph screening using near-infrared spectroscopy. *Anal. Chem*. **75**: 5267–5273

Abrahamsson, C., Johansson, J., Sparén, A., Lindgren, F. (2003) Comparison of different variable selection methods conducted on NIR transmission measurements on intact tablets. *Chemom. Intell. Lab. Syst*. **69**: 3–12

Airaksinen, S., Luukkonen, P., Jørgensen, A., Karjalainen, M., Rantanen, J., Yliruusi, J. (2003) Effects of excipients on hydrate formation in wet masses containing theophylline. *J. Pharm. Sci*. **92**: 516–528

Alcalá, M., Blanco, M., (2006) Content uniformity and tablet hardness testing of intact pharmaceutical tablets by near infrared spectroscopy: A contribution to process analytical technologies. *Anal. Chim. Acta* **557**: 353–359

Aldridge, P., Evans, C., Ward, H., Colgan, S., Boyer, N., Gemperline, P. (1996) Near-IR detection of polymorphism and process-related substances. *Anal. Chem*. **68**: 997–1002

Andersson, M., Josefson, M., Langkilde, F., Wahlund, K.-G. (1999) Monitoring of film coating process for tablets using near infrared reflectance spectroscopy. *J. Pharm. Biomed. Anal*. **20**: 27–37

Andersson, M., Folestad, S., Gottfries, J., Johansson, M., Josefson, M., Wahlund, K.-G. (2000) Quantitative analysis of film coating process by in-line NIR spectrometry and multivariate batch calibration. *Anal. Chem*. **72**: 2099–2108

Andersson, M., Svensson, O., Folestad, S., Josefson, M., Wahlund, K.-G. (2005) NIR spectroscopy on moving solids using a scanning grating spectrometer-impact on multivariate process analysis. *Chemom. Intell. Lab. Syst*. **75**: 1–11

Armenta, S., Moros, J., Garrigues, S., de la Guardia, M. (2005) Automated Fourier transform near infrared determination of buprofezin in pesticide formulations. *Near Infrared Spectrosc*. **13**: 161–168

Bai, S., Nayar, R., Carpenter, J. F., Manning, M. C. (2005) Noninvasive determination of protein conformation in the solid state using near infrared (NIR) spectroscopy. *J. Pharm. Sci*. **94**: 2030–2038

Balboni, M. L. (2003) Process analytical technology – concepts and principles. *Pharm. Technol*. **27**: 54, 56, 58, 60, 62, 64, 66, 254

Beebe, K. R., Pell, R. J., Seasholtz, M. B. (1998) *Chemometrics. A practical guide*. John Wiley & Sons, Inc., New York, NY

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

Berntsson, O., Danielsson, L.-G., Folestad, S. (1998) Estimation of effective sample size when analysing powders with diffuse reflectance near-infrared spectrometry. *Anal. Chim. Acta* **364**: 243–251

Blanco, M., Alcalá, M. (2006) Simultaneous quantitation of five active principles in a pharmaceutical preparation: Development and validation of a near infrared spectroscopic method. *Eur. J. Pharm. Sci*. **27**: 280–286

Blanco, M., Romero, M. A. (2001) Near-infrared libraries in the pharmaceutical industry: a solution for identity confirmation. *Analyst* **126**: 2212–2217

Blanco, M., Villar, A. (2003) Development and validation of a method for the polymorphic analysis of pharmaceutical preparations using near infrared spectroscopy. *J. Pharm. Sci*. **92**: 823–830

Blanco, M., Coello, J., Iturriaga, H., Maspoch, S., Rovira, E. (1997) Determination of water in ferrous lactate by near infrared reflectance spectroscopy with a fibre-optic probe. *J. Pharm. Biomed. Anal*. **16**: 255–262

Blanco, M., Coello, J., Iturriaga, H., Maspoch, S., de la Pezuela, C. (1998) Near-infrared spectroscopy in pharmaceutical industry. *Analyst* **123**: 135R–150R

Blanco, M., Coello, J., Eustaquio, A., Iturriaga, H., Maspoch, S. (1999) Development and validation of a method for the analysis of a pharmaceutical preparation by near infrared diffuse reflectance spectroscopy. *J. Pharm. Sci*. **88**: 551–556

Blanco, M., Valdés, D., Llorente, I., Bayod, M. (2005) Application of NIR spectroscopy in polymorphic analysis: Study of pseudo-polymorphs stability. *J. Pharm. Sci*. **94**: 1336–1342

Blaser, W., Bredeweg, R., Harner, R., LaPack, M., Leugers, A., Martin, D., Pell, R., Workman, J., Wright, L. (1995) Process analytical chemistry. *Anal. Chem*. **67**: 47R–70R

Bodson, C., Dewe, W., Hubert, Ph., Delattre, L. (2006) Comparison of FT-NIR transmission and UV-vis spectrosphotometry to follow the mixing and to assay low dose tablets containing riboflavin. *J. Pharm. Biomed. Anal*. **41**: 783–790

Browne, H. J., Olsson, K. I. (1998) Discussion of control systems in pharmaceutical manufacturing. *Pharm. Eng*. **18**: 84–92

Buckton, G., Yonemochi, E., Hammond, J., Moffat, A. (1998) The use of near infra-red spectroscopy to detect changes in the form of amorphous and crystalline lactose. *Int. J. Pharm*. **168**: 231–241

Buckton, G., Yonemochi, E., Yoon, W. L., Moffat, A. (1999) Water sorption and near IR spectroscopy to study the differences between microcrystalline cellulose and silicified microcrystalline cellulose before and after wet granulation. *Int. J. Pharm*. **181**: 41–47

Bugay, D. (2001) Characterization of the solid-state: spectroscopic techniques. *Adv. Drug Del. Rev*. **48**: 43–65

Buice, R., Gold, T., Lodder, R., Digenis, G. (1995) Determination of moisture in intact gelatin capsules by near-infrared spectroscopy. *Pharm. Res*. **12**: 161–163

Buijs, K., Choppin, G. R. (1963) Near-infrared studies of the structure of water. I. Pure Water. *J. Chem. Phys*. **39**: 2035–2041

Callis, J., Illman, D., Kowalski, B. (1987) Process analytical chemistry. *Anal. Chem*. **59**: 624A–637A

Candolfi, A., Massart, D. L. (2000) Model updating for the identification of NIR spectra from a pharmaceutical excipient. *Appl. Spectrosc*. **54**: 48–53

Chalmers, J. M., Griffiths, P. R. (2002) *Handbook of vibrational spectroscopy. Theory and instrumentation*. John Wiley & Sons, Ltd, Chichester, UK

Chalus, P., Roggo, Y., Walter, S., Ulmschneider, M. (2005) Near-infrared determination of active substance content in intact low-dosage tablets. *Talanta* **66**: 1294–1302

Ciurczak, E. W., Drennen, J. K. III. (2002) *Pharmaceutical and medical applications of near-infrared spectroscopy (Practical spectroscopy)*. Marcel Dekker Inc., New York, NY, pp 192

Ciurczak, E. W., Torlini, R. P., Demkowicz, M. P. (1986) Determination of particle size of pharmaceutical raw materials using near-infrared reflectance spectroscopy. *Spectroscopy* **1**: 36–39

Clarke, F. C. (2004) Extracting process-related Information from pharmaceutical dosage forms using near-infrared microscopy. *Vibr. Spectrosc*. **34**: 25–35

Cleve, E., Bach, E., Schollmeyer, E. (2000) Using chemometric methods and NIR spectrophotometry in the textile industry. *Anal. Chim. Acta* **420**: 163–167

Columbano, A., Buckton, G., Wikeley, P. (2002) A study of the crystallisation of amorphous salbutamol sulphate using water vapour sorption and near infrared spectroscopy. *Int. J. Pharm*. **237**: 171–178

Cogdill, R. P., Drennan III, J. K. (2005) Near infrared spectroscopy in the pharmaceutical industry. *NIR News* **16**: 23–26.

Cogdill, R. P., Anderson, C. A., Drennen, J. K. III (2004) Using NIR spectroscopy as an integrated PAT tool. *Spectroscopy* **19**: 104–109

Cogdill, R. P., Anderson, C. A., Delgado-Lopez, M., Molseed, D., Chisholm, R., Bolton, R., Herkert, T., Afnan, A. M., Drennen, J. K. III (2005a) Process analytical technology case study part I: feasibility studies for quantitative near-infrared method development. *AAPS PharmSciTech*. **6**: E262–E272

Cogdill, R. P., Anderson, C. A., Delgado, M., Chisholm, R., Bolton, R., Herkert, T., Afnan, A. M., Drennen, J. K. III (2005b) Process analytical technology case study part II: development and validation of quantitative near-infrared calibrations in support of a process analytical technology application for real-time release. *AAPS PharmSciTech*. **6**: E273–E283

Cogdill, R. P., Anderson, C. A., Drennen, J. K. III (2005c) Process analytical technology case study, part III: calibration monitoring and transfer. *AAPS PharmSciTech*. **6**: E284–E297

Cui, X., Zhang, Z., Ren, Y., Liu, S., Harrington, P. B. (2004) Quality control of the powder pharmaceutical samples of sulfaguanidine by using NIR reflectance spectrometry and temperature-constrained cascade correlation networks. *Talanta* **64**: 943–948

Curcio, J. A., Petty, C. C. (1951) The near infrared absorption spectrum of liquid water. *J. Optic. Soc. Am*. **41**: 302–304

Delwiche, S., Pitt, R., Norris, K. (1991) Examination of starch-water and cellulose-water interactions with near infrared (NIR) diffuse reflectance spectroscopy. *Starch/Stärke* **43**: 415–422

Dempster, M. A., MacDonald, B. F., Gemperline, P. J., Royer, N. R. (1995) A near infrared reflectance analysis method for the non-invasive identification of film-coated and non-film coated, blister packed tablets. *Anal. Chim. Acta*. **310**: 43–51

Derksen, M. W. J., van de Oetelaar, P. J. M., Maris, F. A. (1998) The use of near-infrared spectroscopy in the efficient prediction of the residual moisture of a freeze-dried product. *J. Pharm. Biomed. Anal*. **17**: 473–480

Donoso, M., Ghaly, E. S. (2005) Prediction of tablets disintegration times using near-infrared diffuse reflectance spectroscopy as a nondestructive method. *Pharm. Dev. Tech*. **10**: 211–217

Dreassi, E., Ceramelli, G., Corti, P., Lonardi, S., Perruccio, P. L. (1995) Near-infrared reflectance spectrometry in the determination of the physical state of primary materials in pharmaceutical production. *Analyst* **120**: 1005–1008

Dreassi, E., Ceramelli, G., Corti, P., Perruccio, P., Lonardi, S. (1996) Application of near-infrared reflectance spectrometry to the analytical control of pharmaceuticals: ranitidine hydrochloride tablet production. *Analyst* **121**: 219–222

Drennen, J. K., Lodder, R. A. (1990) Nondestructive near-infrared analysis of intact tablets for determination of degradation products. *J. Pharm. Sci*. **79**: 622–627

Dyrby, M., Engelsen, S. B., Nørgaard, L., Bruhn, M., Lundsberg-Nielsen, L. (2002) Chemometric quantitation of the active substance (containing C≡N) in a pharmaceutical tablet using near-infrared (NIR) transmittance and NIR FT-Raman spectra. *Applied Spectroscopy* **56**: 579–585

El-Hagrasy, A. S., D'Amico, F., Drennen, J. K. III (2006a) A Process Analytical Technology approach to near-infrared process control of pharmaceutical powder blending. Part I: D-optimal design for characterization of powder mixing and preliminary spectral data evaluation. *J. Pharm. Sci*. **95**: 392–406

El-Hagrasy, A. S., Delgado-Lopez, M., Drennen, J. K. III (2006b) A Process Analytical Technology approach to near-infrared process control of pharmaceutical powder blending: Part II: Qualitative near-infrared models for prediction of blend homogeneity. *J. Pharm. Sci*. **95**: 407–421

El-Hagrasy, A. S., Drennen, J. K. III (2006c) A Process Analytical Technology approach to near-infrared process control of pharmaceutical powder blending. Part III: Quantitative near-infrared calibration for prediction of blend homogeneity and characterization of powder mixing kinetics. *J. Pharm. Sci*. **95**: 422–434

Ellis, S. (2005) Post-tabletting NIR analysis: a look at PAT applicability to the output end of solid dosage forms. *G.I.T. Lab. J., Europe* **9**: 10–12

The European Agency for the Evaluation of Medicinal Products, February 2003, Note for Guidance, EMEA/CVMP/961/01, CPMP/QWP/3309/01 (http://www.emea.eu.int/pdfs/human/qwp/330901en.pdf).

FDA (2004a) PAT: A framework for innovative pharmaceutical development, manufacturing, and quality assurance, Guidance for industry (www.fda.gov/cder/guidance/6419fnl.pdf)

FDA (2004b) Pharmaceutical cGMPs for the 21st Century – A risk-based approach final report (www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm)

Fearn, T. (2005) Chemometrics: an enabling tool for NIR. *NIR News* **16**: 17–19

Feng, Y.-C., Hu, C.-Q. (2006) Construction of universal quantitative models for determination of roxithromycin and erythromycin ethylsuccinate in tablets from different manufacturers using near infrared reflectance spectroscopy. *J. Pharm. Biomed. Anal*. **41**: 373–384

Feudale, R. N., Woody, N. A., Tan, H., Myles, A. J., Brown, S. D., Ferré, J. (2002) Transfer of multivariate calibration models: a review. *Chemom. Intell. Lab. Syst*. **64**: 181–192

Févotte, G., Calas, J., Puel, F., Hoff, C. (2004) Applications of NIR spectroscopy to monitoring and analyzing the solid state during industrial crystallization processes. *Int. J. Pharm*. **273**: 159–169

Fornes, V., Chaussidon, J. (1978) An interpretation of the evolution with temperature of the v2+v3 combination band in water. *J. Chem. Phys*. **68**: 4667–4671

Frake, P., Greenhalgh, D., Grierson, S. M., Hempenstall, J. M., Rudd, D. R. (1997) Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy. *Int. J. Pharm*. **151**: 75–80

Frake, P., Gill, I., Luscombe, C. N., Rudd, D. R., Waterhouse, J., Jayasooriya, U. A. (1998) Near-infrared mass median particle size determination of lactose monohydrate, evaluating several chemometric approaches. *Analyst* **123**: 2043–2046.

Goebel, S. G., Steffens, K.-J. (1998) Online-messung der Produktfeuchte und Korngröße in der Wirbelschnicht mit der Nah-Infrarot-Spektroskopie. *Pharm. Ind*. **60**: 889–895

Gombás, Á., Antal, I., Szabó-Révész, P., Marton, S., Erõs, I. (2003) Quantitative determination of crystallinity of alpha-lactose monohydrate by Near Infrared Spectroscopy (NIRS). *Int. J. Pharm*. **256**: 25–32

Good Manufacturing Practice (1997) *Medicinal products for human and veterinary use*. European Commission, Brussels

Gottfries, J., Depui, H., Fransson, M., Jongeneelen, M., Josefson, M., Langkilde, F. W., Witte, D. T.(1993) Vibrational spectrometry for the assessment of active substance in metoprolol tablets: a

comparison between transmission and diffuse reflectance near-infrared spectrometry. *J. Pharm. Biomed. Anal*. **14**: 1495–1503

Green, R. L., Thurau, G., Pixley, N. C., Mateos, A., Reed, R. A., Higgins, J. P. (2005) In-line monitoring of moisture content in fluid bed dryers using near-IR spectroscopy with consideration of sampling effects on method accuracy. *Anal. Chem*. **77**: 4515–4522

Gupta, A., Peck, G. E., Miller, R. W., Morris, K. M. (2005) Influence of ambient moisture on the compaction behavior of microcrystalline cellulose powder undergoing uni-axial compression and roller-compaction: a comparative study using near-infrared spectroscopy. *J. Pharm. Sci*. **94**: 2301–2313

Hailey, P. A., Doherty, P., Tapsell, P., Oliver, T., Aldridge, P. K. (1996) Automated system for the online monitoring of powder blending processes using near-infrared spectroscopy Part I. System development and control. *J. Pharm. Biomed. Anal*. **14**: 551–559

Han, S. M., Faulkner, P. G. (1996) Determination of SB 216469-S during tablet production using nearinfrared reflectance spectroscopy. *J. Pharm. Biomed. Anal*. **14**: 1681–1689

Harris, S. C., Walker, D. S. (2000) Quantitative real-time monitoring of dryer effluent using fiber optic near-infrared spectroscopy. *J. Pharm. Sci*. **89**: 1180–1186

Hassel, D., Bowman, E. (1998) Process analytical chemistry for spectroscopists. *Applied Spectroscopy* **52**: 18A–29A

Herkert, T., Prinz, H., Kovar, K.-A. (2001) One hundred percent online identity check of pharmaceutical products by near-infrared spectroscopy on the packaging line. *Eur. J. Pharm. Biopharm*. **51**: 9–16

Herschel, W. (1800) Investigation of the powers of the prismatic colours to heat and illuminate objects; with remarks, that prove the different refrangibility of radiant heat. To which is added, an inquiry into the method of viewing the sun advantageously, with telescopes of large apertures and high magnifying powers. *Phil. Trans. R. Soc*. **90**: 255–283

Hogan, S. E., Buckton, G. (2001) The application of near infrared spectroscopy and dynamic vapour sorption to quantify low amorphous contents of crystalline lactose. *Pharm. Res*. **18**: 112–116

ICH Harmonised Tripartite Guideline: Q2A Text on Validation of Analytical Procedures (1994)

ICH Harmonised Tripartite Guideline: Q2B Validation of Analytical Procedures: Methodology (1996)

ICH Harmonised Tripartite Guideline –Pharmaceutical Development Q8 (2005)

Ilari, J. L., Martens, H., Isaksson, T. (1988) Determination of particle size in powders by scatter correction in diffuse near-infrared reflectance. *Applied Spectroscopy* **42**: 722–728

Iwamoto, M., Uozumi, J., Nishinari, K. (1987) Preliminary investigation of the state of water in foods by near infrared spectroscopy. Budapest: *Int. NIR/NIT Conference*, pp 3–12

Jones, J. A., Last, I. R., Macdonald, B. F., Prebble, K. A. (1993) Development and transferability of nearinfrared methods for determination of moisture in a freeze-dried injection product. *J. Pharm. Biomed. Anal*. **11**: 1227–1231

Jørgensen, A., Rantanen, J., Karjalainen, M., Khriachtchev, L., Räsänen, E., Yliruusi, J. (2002) Hydrate formation during wet granulation studied by spectroscopic methods and multivariate analysis. *Pharm. Res*. **19**: 1282–1288

Jørgensen, A. C, Airaksinen, S., Karjalainen, M., Luukkonen, P., Rantanen, J., Yliruusi, J. (2004a) Role of excipients in hydrate formation kinetics of theophylline in wet masses studied by near-infrared spectroscopy. *Eur. J. Pharm. Sci*. **23**: 99–104

Jørgensen, A. C, Luukkonen, P., Rantanen, J., Schaefer, T., Juppo, A. M., Yliruusi, J. (2004b) Comparison of torque measurements and near-infrared spectroscopy in characterization of a wet granulation process. *J. Pharm. Sci*. **93**: 2232–2243

Jørgensen, A., Rantanen, J., Luukkonen, P., Laine, S., Yliruusi, J. (2004c) Visualization of a pharmaceutical unit operation: wet granulation. *Anal. Chem*. **76**: 5331–5338

Kamat, M. S., Lodder, R. A., DeLuca, P. P. (1989) Near-infrared spectroscopic determination of residual moisture in lyophilized sucrose through intact glass vials. *Pharm. Res*. **6**: 961–965

Kirsch, J. D., Drennen, J. K. (1999) Nondestructive tablet hardness testing by near-infrared spectroscopy: a new and robust spectral best-fit algorithm. *J. Pharm. Biomed. Anal*. **19**: 351–362

Kleinebudde, P. (2004) Roll compaction/dry granulation: pharmaceutical applications. *Eur. J. Pharm. Biopharm*. **58**: 317–326

Laasonen, M., Harmia-Pulkkinen, T., Simard, C., Räsänen, M., Vuorela, H. (2003) Development and validation of a near-infrared method for the quantitation of caffeine in intact single tablets. *Anal. Chem*. **75**: 754–760

Last, I. R., Prebble, K. A. (1993) Suitability of near-infrared methods for the determination of moisture in a freeze-dried injection product containing different amounts of the active ingredient. *J. Pharm. Biomed. Anal*. **11**: 1071–1076

Lavine, B. (1998) Chemometrics. *Anal. Chem*. **70**: 209R–228R

Lavine, B. (2000) Chemometrics. *Anal. Chem*. **72**: 91R–98R

Leion, H., Folestad, S., Josefson, M., Sparén, A. (2005) Evaluation of basic algorithms for transferring quantitative multivariate calibrations between scanning grating and FT NIR spectrometers. *J. Pharm. Biomed. Anal*. **37**: 47–55

Li, W., Worosila, G. D. (2005) Quantitation of active pharmaceutical ingredients and excipients in powder blends using designed multivariate calibration models by near-infrared spectroscopy. *Int. J. Pharm*. **295**: 213–219

Li, W., Worosila, G. D., Wang, W., Mascaro, T. (2005) Determination of polymorph conversion of an active pharmaceutical ingredient in wet granulation using NIR calibration models generated from the premix blends. *J. Pharm. Sci*. **94**: 2800–2806

List, K., Steffens, K.-J. (1996) Überwachung und Steuerung von Granulationsprozessen mit Hilfe der Nah-Infrarot-Spektroskopie. *Pharm. Ind*. **58**: 347–353

Lopes, J. A., Costa, P. F., Alves, T. P., Menezes, J. C. (2004) Chemometrics in bioprocess engineering: process analytical technology (PAT) applications. *Chemom. Intell. Lab. Syst*. **74**: 269–275

Lowry, S. R., Hyatt, J., MacCarthy, W. J. (2000) Determination of the wavelength accuracy in the near infrared spectral region based on NIST's infrared transmission wavelength standard SRM 1921. *Appl. Spectros*. **54**: 450–455

Luck, W. A. P. (1976) Hydrogen bonds in liquid water. In: *The hydrogen bond*. Schuster, P., Zundel, G., Sandorfy, C. (eds), North Holland Publishing Co, Amsterdam, Holland, pp 1369–1423

Luner, P., Majuru, S., Seyer, J., Kemper, M. (2000) Quantifying crystalline form composition in binary powder mixtures using near-infrared reflectance spectroscopy. *Pharm. Dev. Technol*. **5**: 231–246

Luukkonen, P., Rantanen, J., Mäkelä, K., Räsänen, E., Tenhunen, J., Yliruusi, J. (2001) Characterization of wet massing behavior of silicified microcrystalline cellulose and α-lactose monohydrate using nearinfrared spectroscopy. *Pharm. Dev. Technol*. **6**: 1–9

MacDonald, B. F., Prebble, K. A. (1993) Some applications of near-infrared reflectance analysis in the pharmaceutical industry. *J. Pharm. Biomed. Anal*. **11**: 1077–1085

Maeda, H., Ozaki, Y., Tanaka, M., Hayashi, N., Kojima, T. (1995) Near infrared spectroscopy and chemometrics studies of temperature-dependent spectral variations of water: relationship between spectral changes and hydrogen bonds. *J. Near Infrared Spectrosc*. **3**: 191–201

Martens, H., Næs, T. (1989) *Multivariate calibration*. 1st edn, John Wiley & Sons Ltd, UK, pp 314–354

McArdle, P., Gilligan, K., Cunningham, D., Ryder, A. (2005) Determination of the polymorphic forms of bicifadine hydrochloride by differential scanning calorimetry-thermogravimetric analysis, X-ray powder diffraction, attenuated total reflectance-infrared spectroscopy, and attenuated total reflectance-near-infrared spectroscopy. *Applied Spectroscopy* **59**: 1365–1371

Moffat, A. C., Trafford, A. D., Jee, R. D., Graham, P. (2000) Meeting of the International Conference on Harmonisation. Guidelines on validation of analytical procedures: Quantification as exemplified by a near infrared reflectance assay of paracetamol in intact tablets. *Analyst* **125**: 1341–1351

Morisseau, K. M., Rhodes, C. T. (1997) Near-infrared spectroscopy as a nondestructive alternative to conventional tablet hardness testing. *Pharm. Res*. **14**: 108–111

Morris, K., Stowell, J., Byrn, S., Placette, A., Davis, T., Peck, G. (2000) Accelerated fluid bed drying using NIR monitoring and phenomenological modeling. *Drug Dev. Ind. Pharm*. **26**: 985–988

Norris, T., Aldridge, P. K. (1996) End-point determination on-line and reaction co-ordinate modelling of homogeneous and heterogeneous reactions in principal component space using periodic near-infrared monitoring. *Analyst* **121**: 1003–1008

Norris, K. H., Williams, D. C. (1983) Optimization of mathematical treatments of raw near-infrared signal in the measurement of protein in hard red spring wheat. I. Influence of particle size. *Cereal Chem*. **61**: 158–165

Norris, T., Aldridge, P. K., Sekulic, S. S. (1997) Determination of endpoints for polymorph conversions of crystalline organic compounds using on-line near-infrared spectroscopy. *Analyst* **122**: 549–552

O'Neil, A., Jee, R., Moffat, A. (1998) The application of multiple linear regression to the measurement of the median particle size of drugs and pharmaceutical excipients by near-infrared spectroscopy. *Analyst* **123**: 2297–2302

O'Neil, A., Jee, R., Moffat, A. (1999) Measurement of cumulative particle size distribution of microcrystalline cellulose using near infrared reflectance spectroscopy. *Analyst* **124**: 33–36

Osborne, B. G., Fearn, T., Hindle, P. H. (1993) *Practical NIR spectroscopy with applications in food and beverage industry analysis*. 2nd edn, Longman, Harlow, UK.

Otsuka, M. (2004) Comparative particle size determination of phenacetin bulk powder by using Kubelka–Munk theory and principal component regression analysis based on near-infrared spectroscopy. *Powder Technol*. **141**: 244–250

Otsuka, M. (2006) Chemoinformetrical evaluation of granule and tablet properties of pharmaceutical preparations by near-infrared spectroscopy. *Chemom. Intelll. Lab. Syst*, In press

Parisi, A. F., Nogueiras, L., Prieto, H. (1990) On-line determination of fuel quality parameters using near infrared spectrometry with fibers optics and multivariate calibration. *Anal. Chim. Acta*. **238**: 95–100

Parris, J., Airiau, C., Escott, R., Rydzak, J., Crocombe, R. (2005) Monitoring API drying operations with NIR. *Spectroscopy* **20**: 34, 36, 38, 40, 42

Pasquini, C. (2003) Near infrared spectroscopy: fundamentals, practical aspects and analytical applications. *J. Braz. Chem. Soc*. **14**: 198–219

Patel, A. D., Luner, P. E., Kemper, M. S. (2000) Quantitative analysis of polymorphs in binary and multi-component powder mixtures by near-infrared reflectance spectroscopy. *Int. J. Pharm*. **206**: 63–74

Pérez-Ramos, J. D., Findlay, W. P., Peck, G., Morris, K. R. (2005) Quantitative analysis of film coating in a pan coater based on in-line sensor measurements. *AAPS PharmSciTech*. **6**: E127–E136

Ph. Eur. (2001) Near-infrared spectrometry, Chapter 2.2.40. *European Pharmacopoeia*, 4th edn, pp 55–56

Pimental, G. C., McClellan, A. L. (1960) *The hydrogen bond*. W. H. Freeman, San Francisco, CA

Plugge, W., van der Vlies, C. (1993) Near-infrared spectroscopy as an alternative to assess compliance of ampicillin trihydrate with compendial specifications. *J. Pharm. Biomed. Anal*. **11**: 435–442

Plugge, W., van der Vlies, C. (1996) Near-infrared as a tool to improve quality. *J. Pharm. Biomed. Anal*. **14**: 891–898

Radtke, G., Knop, K., Lippold, C. (1999) In-process control of direct pelletisation in the rotary fluidized bed using NIR spectroscopy. *NIR News* **10**: 4–12

Rantanen, J., Yliruusi, J. (1998) Determination of particle size in a fluidized bed granulator with a near infrared set-up. *Pharm. Pharmacol. Commun*. **4**: 73–75

Rantanen, J., Lehtola, S., Rämet, P., Mannermaa, J.-P., Yliruusi, J. (1998) On-line monitoring of moisture content in an instrumented fluidized bed granulator with a multi-channel NIR moisture sensor. *Powder Technol*. **99**: 163–170

Rantanen, J., Antikainen, O., Mannermaa, J.-P., Yliruusi, J. (2000) Use of the near-infrared reflectance method for measurement of moisture content during granulation. *Pharm. Dev. Technol*. **5**: 209–217

Rantanen, J., Räsänen, E., Antikainen, O., Mannermaa, J.-P., Yliruusi, J. (2001) In-line moisture measurement during granulation with a four wavelength near infrared sensor: an evaluation of process related variables and a development of non-linear calibration model. *Chem. Int. Lab. Syst*. **56**: 51–58

Rantanen, J., Wikström, H., Rhea, F. E., Taylor, L. S. (2005a) Improved understanding of factors contributing to quantification of anhydrate/hydrate powder mixtures. *Applied Spectroscopy* **59**: 942–951

Rantanen, J., Wikström, H., Turner, R., Taylor, L. S. (2005b) Use of in-line near-infrared spectroscopy in combination with chemometrics for improved understanding of pharmaceutical processes. *Anal. Chem*. **77**: 556–563

Räsänen, E., Rantanen, J., Jørgensen, A., Karjalainen, M., Paakkari, T., Yliruusi, J. (2001) Novel identification of pseudopolymorfic changes of theophylline during wet granulation using near infrared spectroscopy. *J. Pharm. Sci*. **90**: 389–396

Räsänen, E., Rantanen, J., Mannermaa, J.-P., Yliruusi, J., Vuorela, H. (2003) Dehydration studies using a novel multichamber microscale fluid bed dryer with in-line near-infrared measurement. *J. Pharm. Sci* **92**: 2074–2081

Reeves, J. B., Zapf, C. M. (1999) Spectral library searching: mid infrared versus near infrared spectra for classification of powdered food ingredient. *Appl. Spectrosc*. **53**: 836–844

Reich, G. (2005) Near-infrared spectroscopy and imaging: basic principles and pharmaceutical applications. *Adv. Drug. Deliv. Rev*. **57**: 1109–1143

Rodrigues, L. O., Marques, J. L., Cardoso, J. P., Menezes, J. C. (2005) A PAT application on an API crystallization process. *PAT-The Journal of Process Analytical Technology* **2**: 12–17, 32

Roggo, Y., Roeseler, C., Ulmschneider, M. (2004) Near infrared spectroscopy for qualitative comparison of pharmaceutical batches. *J. Pharm. Biomed. Anal*. **36**: 777–786

Roggo, Y., Jent, N., Edmond, A., Chalus, P., Ulmschneider, M. (2005) Characterizing process effects on pharmaceutical solid forms using near-infrared spectroscopy and infrared imaging. *Eur. J. Pharm. Biopharm*. **61**: 100–110

Rowe, R., Roberts, R. (1998) In: *Intelligent software for product formulation*. Taylor & Francis Ltd, London, UK, p. 250

Sandler, N., Rantanen, J., Heinämäki, J., Römer M., Marvola, M., Yliruusi, J. (2005) Pellet manufacturing by extrusion-spheronization using process analytical technology. *AAPS PharmSciTech* **6**: E174–183

Sasic, S., Ozaki, Y. (2001) Short wave near infrared spectroscopy of biological fluid. 1. Quantitative analysis of fat, protein, and lactose in raw milk by partial Least Squares regression and band assignment. *Anal. Chem*. **73**: 64–71

Sekulic, S. S., Ward, H. W., Brannegan, D. R., Stanley, E. D., Evans, C. L., Sciavolino, S. T., Hailey, P. A., Aldridge, P. K. (1996) On-line monitoring of powder blend homogeneity by near-infrared spectroscopy. *Anal. Chem*. **68**: 509–513

Sekulic, S. S., Wakeman, J., Doherty, P., Hailey, P. A. (1998) Automated system for the online monitoring of powder blending processes using near-infrared spectroscopy Part II. Qualitative approaches to blend evaluation. *J. Pharm. Biomed. Anal.* **17**: 1285–1309

Seyer, J., Luner, P., Kemper, M. (2000) Application of diffuse reflectance near-infrared spectroscopy for determination of crystallinity. *J. Pharm. Sci.* **89**: 1305–1316

Schimleck, L. R., Stürzenbecher, R., Jones, P. D., Evans, R. (2004) Development of wood property calibrations using near infrared spectra having different spectral resolutions. *J. Near Infrared Spectrosc.* **12**: 55–61

Skibsted, E. T. S., Boelens, H. F. M., Westerhuis, J. A., Witte, D. T., Smilde, A. K. (2006) Simple assessment of homogeneity in pharmaceutical mixing processes using a near-infrared reflectance probe and control charts. *J. Pharm. Biomed. Anal.* **41**: 26–35

Sinsheimer, J. E., Poswalk, N. M. (1968) Pharmaceutical applications of the near infrared determination of water. *J. Pharm. Sci.* **57**: 2007–2010

Sowa, M. G., Payette, J. R., Mantsch, H. H. (1999) Near infrared spectroscopic assessment of tissue hydration following surgery. *J. Surg. Res.* **86**: 62–69

Stein, H. H., Ambrose, J. M. (1963) Near-infrared method for determination of water in aluminium aspirin. *Anal. Chem.* **35**: 550–552

Stordrange, L., Rajalahti, T., Libnau, F. O. (2004) Multiway methods to explore and model NIR data from a batch process. *Chemom Intell. Lab. Syst.* **70**: 137–145

Tran, C. D. (2005) Principles, instrumentation and applications of infrared multispectral imaging, an overview. *Anal. Lett.* **38**: 735–752

Ufret, C., Morris, K. (2001) Modeling of powder blending using on-line near-infrared measurements. *Drug Dev. Ind. Pharm.* **27**: 719–729

USP (2003) Near-infrared spectrophotometry, Chapter 1119. *United States Pharmacopoeia USP26NF21*: 2388–2391

Vredenbregt, M. J., Blok-Tip, L., Hoogerbrugge, R., Barends, D. M., de Kaste, D. (2006) Screening suspected counterfeit Viagra® and imitations of Viagra® with near-infrared spectroscopy. *J. Pharm. Biomed. Anal.* **40**: 840–849

Wang, Q., Dejesus, S., Conzen, J. P., Schmidt, A., Weiler, H. (1998) Calibration transfer in near infrared analysis of liquids and solids. *J. Near Infrared Spectrosc.* **6**: A201–A205

Wargo, D. J., Drennen, J. K. (1996) Near infrared spectroscopic characterization of pharmaceutical powder blends. *J. Pharm. Biomed. Anal.* **14**: 1415–1423

Watano, S., Terashita, K., Miyanami, K. (1990) Development and application of infrared moisture sensor to complex granulation. *Bull. Univ. Osaka. Pref., Series A*, **39**: 187–197

Westenberger, B. J. Ellison, C. D. Fussner, A. S., Jenney, S., Kolinski, R. E., Lipe, T. G., Lyon, R. C., Moore, T. W., Revelle, L. K., Smith, A. P., Spencer, J. A., Story, K. D., Toler, D. Y., Wokovich, A. M., Buhse, L. F. (2005) Quality assessment of internet pharmaceutical products using traditional and non-traditional analytical techniques. *Int. J. Pharm.* **306**: 56–70

White, J. (1994) On-line moisture detection for a microwave vacuum dryer. *Pharm. Res.* **11**: 728–732

Williams, P., Norris, K. (1987) *Near-infrared technology in the agricultural and food industries*. 1st edn, American Association of Cereal Chemists, Inc., St Paul, MI

Wold, S. (1995) Chemometrics; what do we mean with it, and what do we want from it? *Chemometr. Intell. Lab. Syst.* **30**: 109–115

Workman, J., Jr. (1993) A review of process near infrared spectroscopy: 1980–1994. *J. Near Infrared Spectrosc.* **1**: 221–245

Workman, J., Jr. (1999) Review of process and non-invasive near infrared and infrared spectroscopy: 1993–1999. *Appl. Spectrosc. Reviews* **34**: 1–89

Workman, J., Jr., Veltkamp, D., Doherty, S., Anderson, B., Creasy, K., Koch, M., Tatera, J., Robinson, A., Bond, L., Burgess, L., Bokerman, G., Ullman, A., Darsey, G., Mozayeni, F., Bamberger, J., Greenwood, M. (1999) Process analytical chemistry. *Anal. Chem.* **71**: 121R–180R

Yu, L. X., Lionberger, R. A., Raw, A. S., D'Costa, R., Wu, H. Hussain, A. S. (2004) Applications of process analytical technology to crystallization processes. *Adv. Drug Deliv. Rev.* **56**: 349–369

Yoon, W. L., Jee, R. D., Moffat, A. C. (1998) Optimisation of sample presentation for the near-infrared spectra of pharmaceutical excipients. *Analyst* **123**: 1029–1034

Yoon, W. L., Jee, R. D., Charvill, A., Lee, G., Moffat, A. C. (2004) Application of near-infrared spectroscopy to the determination of the sites of manufacture of proprietary products. *J. Pharm. Biomed. Anal.* **34**: 933–944

Zhou, G. X., Ge, Z. H., Dorwart, J., Izzo, B., Kukura, J., Bicker, G., Wyvratt, J. (2003) Determination and differentiation of surface and bound water in drug substances by near infrared spectroscopy. *J. Pharm. Sci.* **92**: 1058–1065