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Research paper

In-line moisture measurement during granulation with a four-wavelength near infrared sensor: an evaluation of particle size and binder effects

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Abstract

Factors affecting in-line near infrared (NIR) moisture measurement with a four-wavelength sensor were evaluated (choice of binder used in granulation liquid and the increase in particle size). An entire NIR spectrum is not necessary for the measurement of water, and often the use of only a few NIR wavelengths around the water band enables reliable and high-speed detection of moisture. Glass ballotini and microcrystalline cellulose (MCC) were used as model test materials. The binders studied were poly[1-(2-oxo-1-pyrrolidinyl)ethylene] (PVP) and gelatin. Full off-line NIR spectra of test materials at different levels of binder solutions were measured. The major spectral features for both the binders were bands around 1700 nm (first overtones CH related stretches) and 2200 nm (combination bands). Gelatin also had an NH band around 1500 nm (first overtones of NH stretches) and combination bands at about 2050 nm. Particle size effects were observed as an increase in spectra baseline. All these factors should be considered when choosing NIR wavelengths used for detection of water with a fixed wavelength set-up. A robust calibration model enables the development of in-process control of wet granulation processes.

Keywords: Binder; Granulation; Moisture measurement; Near infrared spectroscopy; Particle size

1. Introduction

The recent developments in near infrared (NIR) spectroscopy together with progression of computer performance offers new possibilities. NIR combined with multivariate data analysis opens many interesting perspectives in pharmaceutical analysis. Low absorptivities in the NIR region enable analysis with no sample preparation using the reflectance mode. Consequently, advantages over traditional wet chemistry methods are gained by using the NIR spectral region. NIR has been applied in several process analytical applications within wet granulation of pharmaceutics [1–7]. One of the first pharmaceutical applications of NIR was the measurement of water [8]. Detection of moisture in freeze-dried solids has been reported [9–12].

The NIR spectrum contains overlapping vibrational overtones and combination bands from different CH, NH and OH groups. Fundamental absorption bands are in the mid IR region. The NIR spectrum is affected by the physical properties of the sample. The texture of the particle surface, particle size and density affect the back-reflected light. Analysis of these overlapping and broad bands with displacement of spectra baseline requires effective mathematical treatment [13]. Various mathematical treatments have been suggested for modelling the particle size data with NIR spectra [4,14–18]. Aldridge et al. [19] used NIR to discriminate between different polymorphic forms. Buckton et al. [20] identified changes in the amorphous and crystalline form of lactose non-invasively with NIR. The effect of granulation on the structure of microcrystalline (MCC) and silicified (SMCC) microcrystalline cellulose has been studied using NIR [21].

The measurement of water in the NIR region can be performed with constructions applying only a few measuring wavelengths. In these cases, calibration is performed by combining these measuring wavelengths into a baseline-corrected absorbance value, which is further calibrated against a valid reference technique. In addition to detection of the water signal, the baseline correction signal is needed in order to correct the offset in spectra baseline. In this study, the effect of binder on the NIR moisture measurement

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was evaluated, in addition to the evaluation of the particle size effects. This study was part of the development of a four-wavelength NIR moisture sensor, and the in-line use of the present set-up during fluid bed granulation has been described previously [6,7].

2. Materials and methods

2.1. Materials

The binders studied were poly[1-(2-oxo-1-pyrrolidinyl)ethylene] (PVP) (Plasdone K-25, ISP Technologies Inc., Wayne, NJ) and gelatin (Orion Pharma, Finland). In the first phase, both binders were studied as dry material. PVP was further studied as a solution and as a model binder in granulations. Solutions in purified water were prepared using 10 and 20% w/w of PVP. Glass ballotini (Jencons Ltd., Bedfordshire, UK) of three different particle size distributions and microcrystalline cellulose (MCC) (Emcocel 50M, Penwest Pharmaceuticals, Nastola, Finland) were used as model test materials to which water or PVP solution was added.

2.2. Material characterization

NIR spectra were measured using an Fourier transform (FT)-NIR spectrometer (Bühler NIRVIS, Uzwil, Switzerland) with fibre-optic probe. Diffuse reflectance spectra for solids and transflectance spectra for liquids were measured over the range of 4008–9996 cm^{-1} with a resolution of 12 cm^{-1}. Each individual spectrum was an average of four scans and all measurements were performed five times. The spectral treatment (absorbances and second derivatives) was performed with NIRCAL v. 2.0 (Bühler, Uzwil, Switzerland).

Particle size (median of particle size) and size distributions (10 and 90% fractiles) were determined by a laser light diffractometer (LLD) (Malvern 2600C droplet and particle sizer, Malvern Instruments Ltd., Malvern, UK). The method of determination was particles in air (PIA). Bulk volume was determined by pouring 50 g of material into a 250-ml glass measuring cylinder held at an angle of 45° to the horizontal while pouring. After pouring, the measuring cylinder was brought to a vertical position and the bulk volume was read. Tapped volumes were determined using a standardized tapped density tester (Erweka SVM1, Erweka GmbH, Heusenstamm, Germany) in which the glass measuring cylinder was tapped 500 times.

The true density of materials was measured using a pycnometer (Micromeritics, Model 1305, Norcross, GA). The results are the averages of three triplicate determinations.

The moisture content of the excipients was determined using an infrared dryer (Sartorius Thermocontrol YTC01L, Sartorius GmbH, Göttingen, Germany). It heated the samples (105°C) until the loss of weight was less than 0.1% in 50 s.

3. Results and discussion

3.1. Material characterization

The physical properties of the materials used are listed in Table 1. The inorganic solid model particles (glass ballotini) consisted of spherical and non-porous particles with median diameters of 40 (ballotini A), 280 (ballotini B) and 720 (ballotini C) μm. There were no significant differences in the packing properties of ballotini B and C (packing fraction 0.63). Ballotini A showed more loose packing (packing fraction 0.53). The increase in cohesive forces due to smaller particle size affected the packing of spheres. Similar to organic compounds, gelatin with the larger particle size showed denser packing.

3.2. Spectral evaluation of solid materials and solutions

The NIR spectrum is rich in information, the physicochemical properties of materials may be determined nondestructively. Mathematical treatment is often needed to extract the desired information from the spectrum. The particle size effects were minimized using derivative treatment for spectra. The spectra of five parallel measurements from dry solid materials demonstrate some characteristics of NIR and an effect of mathematical treatment on the spectra (Fig. 1). PVP consists of linear polymers of 1-vinylpyrrolidin-2-one. Gelatin is a binder of natural origin and a hetero-

Table 1
Physical properties of materials

Material	Particle size distribution (μm)[a]	Bulk density[b]	Tapped density[b]	True density[b]	Packing fraction[c]	Moisture content[d]
Gelatin	430 (170–790)	0.60 ± 0.01	0.68 ± 0.01	1.346 ± 0.001	0.45	5.6 ± 0.6
PVP	70 (40–100)	0.33 ± 0.00	0.40 ± 0.00	1.172 ± 0.005	0.28	3.5 ± 0.1
MCC	70 (30–100)	0.30 ± 0.00	0.36 ± 0.00	1.533 ± 0.005	0.20	4.0 ± 0.1
Ballotini A	40 (20–60)	1.23 ± 0.03	1.52 ± 0.01	2.394 ± 0.005	0.51	ND
Ballotini B	280 (240–410)	1.57 ± 0.01	1.65 ± 0.02	2.473 ± 0.002	0.63	ND
Ballotini C	720 (600–1030)	1.55 ± 0.03	1.61 ± 0.01	2.471 ± 0.006	0.63	ND

[a] Values are median (10–90 fractiles) laser light diffraction (mean, $n = 3$).
[b] 10^3 kg m^{-3} (mean ± SD, $n = 3$).
[c] Bulk density/true density.
[d] Loss on drying%, wet basis (mean ± SD, $n = 3$); ND, not determined.

geneous mixture of water-soluble proteins. A significant variation between parallel NIR determinations was noted with gelatin in comparison with synthetic PVP and MCC (Fig. 1, absorbance plots).

The inorganic glass ballotini proved an ideal model compound due to the minimal absorbance in the NIR region. The effect of particle size differences was noticed on the general baseline of spectra. The baseline of apparent absorbance, log(1/*R*), increased when reflectance (*R*) decreased due to the larger particle size. The scattering of the light diminishes and the light penetrates deeper into the solid material with larger particle size and therefore log(1/*R*) increases [22]. Ilari et al. [15] used the Kubelka–Munk transform (Eq. (1)) for linearization of reflectance data.

$$\frac{K}{S} = \frac{(1-R)^2}{2R} \quad (1)$$

where *K* is the absorption coefficient and *S* is the scattering coefficient. They found the same behaviour of *K/S* data of ballotini with increasing particle size. It was further noticed with organic compounds used in this study (Fig. 1) that the particle size effect was strongest for the highest absorbance, log(1/R), values (region between 1900 and 2300 nm). Norris and Williams [23] studied ground wheat samples with a mean particle size varying from 150 to 335 μm. They found the particle size effect to be greater at longer wavelengths, but more dependent on the log(1/*R*) level than
on the wavelength. When the light penetrates deeper into the sample due to the increasing particle size, more absorption occurs and an apparent increase in absorbance is observed. In the present in-line NIR set-up [6,7] the effect of increasing particle size during granulation was minimized using four-wavelength detection around the water band at 1940 nm.

All organic substances had water bands around 1450 nm (first overtone of –OH stretch at 3500 cm^{-1}) and 1940 nm (combination of –OH stretch at 3500 cm^{-1} with –OH deformation at 1645 cm^{-1}). The moisture contents of solid materials are listed in Table 1. Another spectral feature of both the solid binders studied was the CH related overtone bands around 1700 nm (first overtones of CH stretches) and a weaker band around 1200 nm (second overtones of CH stretches) [22]. Two combination bands around 2200 nm were noticed with both the solid binders. This region typically has combinations of CH, OH and CO stretches and deformations. Gelatin also has an NH band around 1500 nm (first overtones of NH stretches) and a combination band at about 2050 nm.

Povidone was further studied as a solution (0, 10, 20 w/w% PVP) and the same CH-related bands were able to be identified (Fig. 2). The second derivative treatment was used for transflectance data, log(1/*T*). Absorbance maxima due to CH bonding were found at 1680, 1725, 2170 and 2270 nm.

3.3. Spectral evaluation of wet masses

The glass ballotini demonstrated spectral phenomena during granulation (Fig. 3a). Water bands around 1450 and 1940 nm were again observed and, as expected, they were a major spectral feature of inorganic ballotini spectra. The change in physical properties of the sample resulted in an upward shift of the spectra baseline. The increase in spectra baseline was due to the change in refractive index discontinuities. The glass–air interfaces (refractive indexes 1.5 and 1.0, respectively) were replaced by glass–water

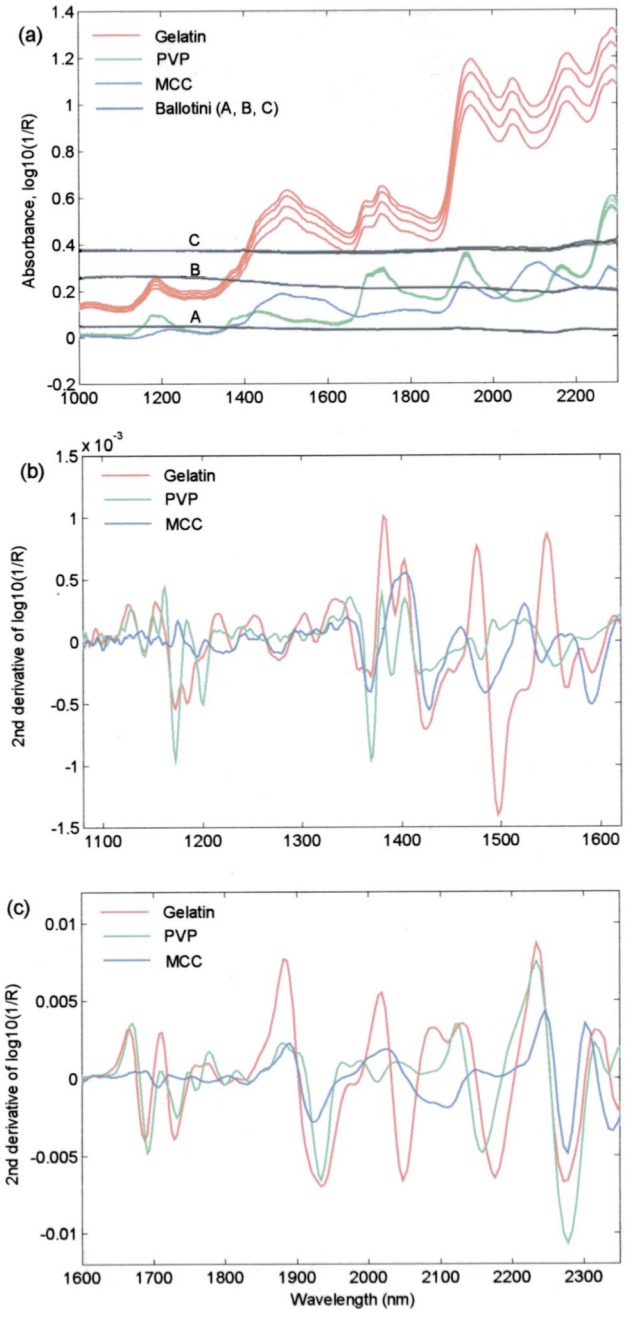

Fig. 1. NIR absorbance spectra (log(1/*R*)) and second derivative of log(1/*R*) of solid materials studied. (a) Absorbance 1000–2300 nm; (b) second derivative of log(1/*R*) 1080–1620 nm; (c) second derivative of log(1/*R*) 1600–2350 nm. Materials indicated with colour: gelatin (red), MCC (blue), PVP (green) and glass ballotini (black, size fraction indicated with A, B and C).

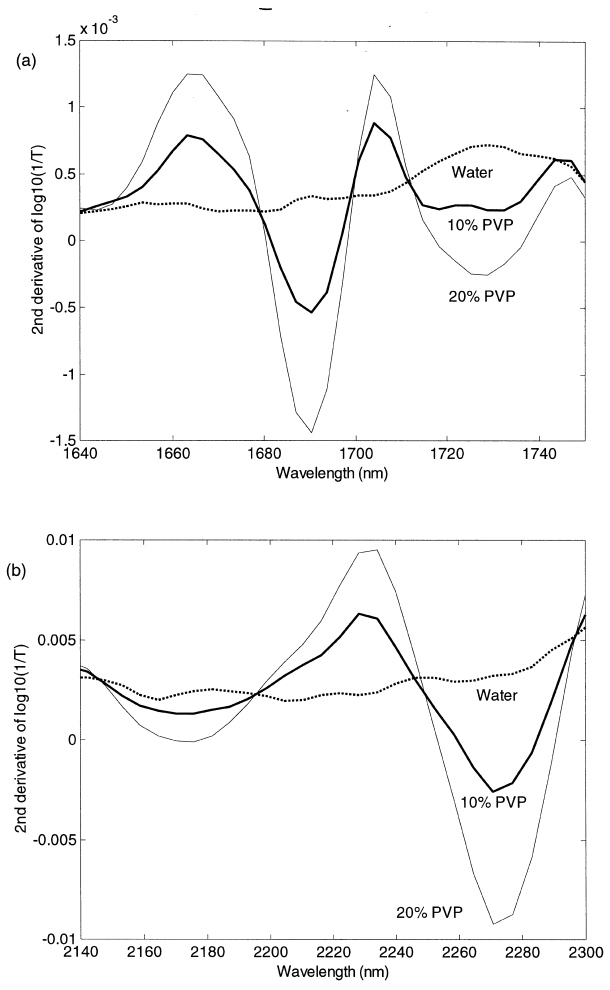

Fig. 2. Second derivative of log(1/*T*) of water and PVP solutions. (a) 1640–1760 nm; (b) 2140–2280 nm.

interfaces (refractive indexes 1.5 and 1.3, respectively). The change in refractive properties affected the effective path-length and resulted in an apparent increase in absorbance, log(1/*R*), in the whole spectra. The same was observed with MCC (Fig. 3b), but not to the same extent. Water within an inorganic test material (glass ballotini) was adsorbed and in the case of an organic test material (MCC), it was absorbed within cellulose fibres. The back reflected light was also affected by the continuous water film around glass ballotini. Changes in reflection and refraction properties of materials can be further described according to Snell's law and Fresnel equations.

The comparison of the second derivative difference spectra of glass ballotini granulated with water and PVP solution enables the identification of binder effects on the NIR spectra of granulated materials (Figs. 4 and 5). The difference spectra were generated by subtracting the spectra of granulated material from that of dry material. The spectral effects of PVP were again identified at around 1700 and 2200 nm (marked with regions I and II, respectively) with glass ballotini (Fig. 4b). When an organic test material with absorbing nature (MCC) was studied (Fig. 5), these effects were not as visible as with the non-absorbing test material (glass ballotini). Effect of binder should also be considered while calibrating the spectral response of an NIR set-up for moisture measurement. Understanding all these factors affecting the back-reflected light is critical when a fixed wavelength system is applied to moisture measurement of pharmaceutics. The signal at 1940 nm is not the only choice for detection of water. The absorbance maxima at 1450 or 970 nm can also be applied. Therefore, it is critical to understand all the binder effects in the NIR region when specifying the selection of measuring wavelengths.

Watano et al. [24] used a fixed-wavelength NIR filter instrument for moisture measurement during the agitation fluid bed granulation. They 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. Understanding the nature of water–solid

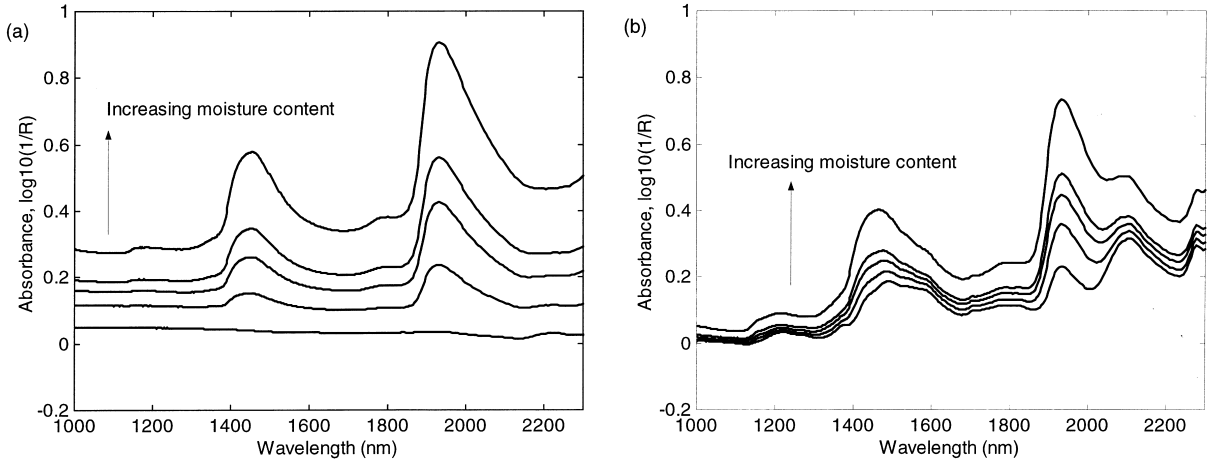

Fig. 3. Effect of increasing moisture content on the NIR absorbance (log(1/*R*)) spectra. (a) Glass ballotini (moisture levels: dry ballotini 3.2, 6.3, 9.1, 14.3 w/w%); (b) MCC (moisture levels: 4.0, 13.1, 20.7, 27.1, 37.3 w/w%).

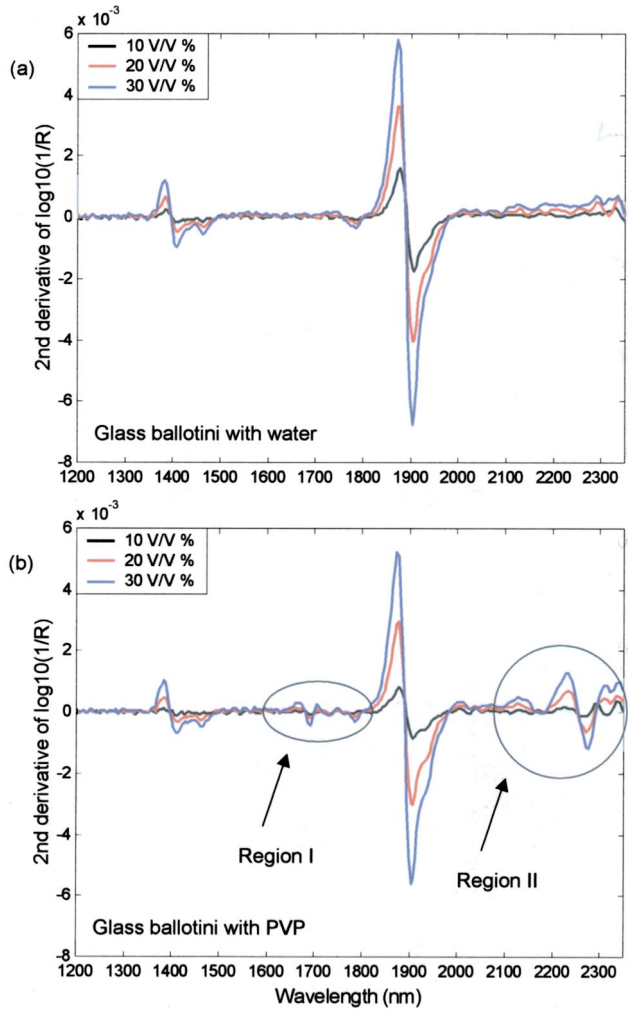

Fig. 4. Second derivative difference spectra of glass ballotini granulated with (a) increasing amount of water; (b) 20 w/w% povidone. Granulation liquid effects on spectra circled (Regions I and II).

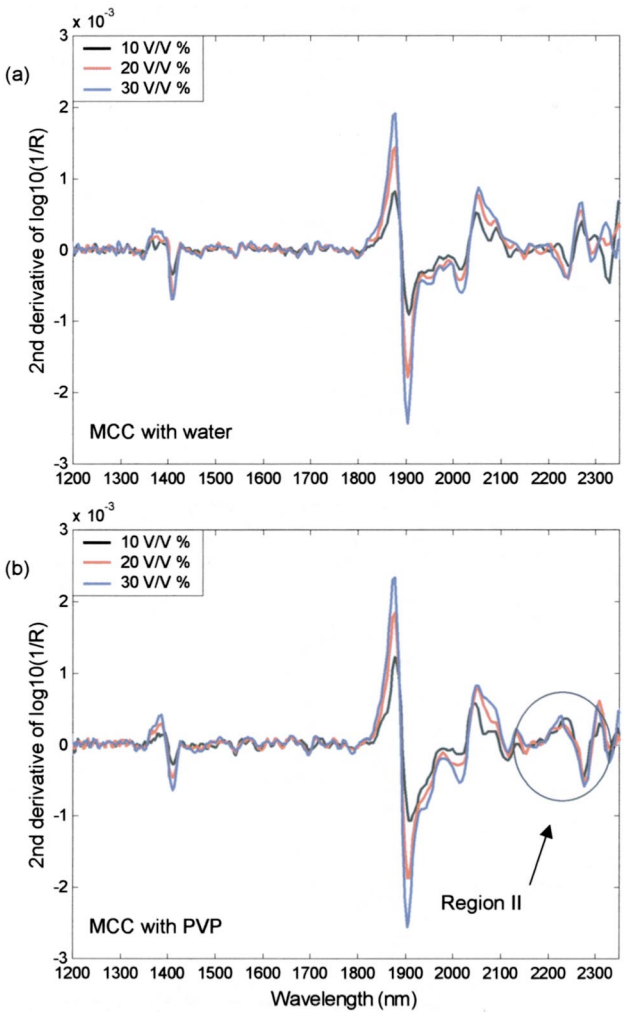

Fig. 5. Second derivative difference spectra of MCC granulated with (a) increasing amount of water; (b) 20 w/w% povidone. Granulation liquid effects on spectra circled (Region II).

interactions is important when the NIR set-up is applied for in-line moisture measurement. In the first phase, studying these interactions is easier when performed off-line. A fixed wavelength multichannel set-up can also be used for moisture measurement during wet granulation process [6,7]. A representative sample set is needed for each formulation to develop a robust calibration that has practical utility. Sampling from process streams is often a difficult and a time-consuming part of the calibration. The use of off-line methods facilitates the development of the calibration for on-line and in-line methods.

4. Conclusions

Calibration of in-line near infrared moisture measurement with a fixed-wavelength set-up requires understanding of all factors affecting the detected signal. Understanding the physicochemical phenomena affecting NIR spectra during granulation enables a reliable choice of wavelengths used for in-line moisture measurement, and the development of a valid calibration model. The full off-line NIR spectra of formulations at different levels of granulation liquid can be used for predicting these phenomena.

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