Pellet Manufacturing by Extrusion-Spheronization Using Process Analytical Technology

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ABSTRACT

The aim of this study was to investigate the 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 behavior of the active pharmaceutical ingredients (APIs) during pelletization. Raman spectroscopy, near-infrared (NIR) spectroscopy, and X-ray powder diffraction (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). Batches were dried at 3 temperature levels (60°C, 100°C, and 135°C). Water induced a hydrate formation in both model formulations during processing. NIR spectroscopy gave valuable real-time data about the state of water in the system, but it was not able to detect the hydrate formation in the theophylline and nitrofurantoin formulations during the granulation, extrusion, and spheronization stages because of the saturation of the water signal. Raman and XRPD measurement results confirmed the expected pseudopolymorphic changes of the APIs in the wet process stages. The relatively low level of Raman signal with the theophylline formulation complicated the interpretation. The drying temperature had a significant effect on dehydration. For a channel hydrate (theophylline), dehydration occurred at lower drying temperatures. In the case of isolated site hydrate (nitrofurantoin), dehydration was observed at higher temperatures. To reach an understanding of the process and to find the critical process parameters, the use of complementary analytical techniques are absolutely necessary when signals from APIs and different excipients overlap each other.

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INTRODUCTION

Drugs are exposed to water in many pharmaceutical processes. The subsequent interaction with water may induce phase transformations in solids. Water molecules associate with solids by various mechanisms.[1] Phase transitions can lead to changes in the pharmaceutical and biopharmaceutical performance of the drug. The bioavailability can change as a result of polymorphic interconversions, desolvation of solvates, alteration of the crystallinity, or formation of hydrates.[2] Morris et al[3] have discussed the theoretical approaches of physical transformations of active pharmaceutical ingredients (APIs) during manufacturing processes. They stated that wet granulation provides an ideal medium for the crystallization of new phases for the API. A number of phase changes or process-induced transformations (PITs) can occur due to the different process steps of wet granulation, which include wetting, mechanical stress, and drying. Granulation or the manufacture of pellets using the extrusion-spheronization technique includes several process stages (blending of the dry mass, wet granulation of the mass, extrusion of the moist mass, rotation of the extrudate by spheronization, and drying). The amount of wetting liquid in the powder mass in pelletization by extrusion-spheronization is relatively high compared with fluidized bed granulation. Consequently, depending on the drug substance and excipients processed, solution-mediated polymorphic transformations probably take place. The effect of the moisture content on process behavior has been studied in terms of obtaining pellets with optimum size and shape characteristics.[4-7] Jerwanska et al[8] have investigated the influence of water content on the porosity and liquid saturation of the extrudate. Baert and Remon[9] studied pellets made by extrusion-spheronization and reported slower release rates of theophylline monohydrate and sulfamethoxazole with increasing amounts of granulation fluid. The differences in release profiles were correlated with the

hardness, density, and structure of the pellets. Pelletization processes have also been studied in terms of the phase transformations of APIs. Herman et al[10-11] have described the transformation of anhydrous theophylline to theophylline monohydrate with elevated humidity levels and, subsequently, decreased drug release rates. Ando et al[12] and Adeyeye et al[13] studied the storage of theophylline tablets under conditions of high humidity. They found that the anhydrate was converted to monohydrate, resulting in decreased drug release rates of theophylline. Debnath and Suryanarayanan[14] recently studied the influence of processing-induced phase transformations on the dissolution of theophylline tablets. They concluded that product performance was a complex function of the physical state of the active and the processing conditions. The polymorphic change of theophylline during wet granulation has also been discussed by Räsänen et al[15] and Morris et al.[3] The choice of excipients has an impact on hydrate formation of theophylline in wet masses.[16] Rodríguez-Hornedo et al[17] have investigated the kinetics of the anhydrous-to-hydrate transformation of theophylline. In addition to theophylline, nitrofurantoin possesses a tendency for phase transitions in different humidity conditions.[18] Pienaar and co-workers have reported the existing polymorphs of nitrofurantoin and discussed some practical implications for formulation of nitrofurantoin.[19-21] Otsuka and Matsuda[22] have investigated the hydration kinetics of anhydrous nitrofurantoin and shown that it is dependant on the excipients used. Otsuka et al[23] studied the dissolution rates of nitrofurantoin and estimated that the solubility of the anhydrous nitrofurantoin was almost 2 times larger than that of the monohydrate.

Pseudopolymorphic changes of drug substances have been monitored successfully using near-infrared (NIR) spectroscopy.[24,15] The use of NIR spectroscopy is fast and involves minimal sample preparation, while leaving the sample undamaged. Jørgensen et al[25] successfully applied CCD Raman spectrometer and NIR to monitor hydrate formation processes of theophylline and caffeine during granulation in a planetary mixer. Nevertheless, X-ray powder diffraction (XRPD) is generally used to confirm polymorph transformations. The implementation of process analytical technology (PAT) has to be supported by a scientifically based process design that identifies key measures of product quality and the critical process variables that affect them to ensure production of final products with the desired quality.[26] In accordance with the Food and Drug Administration's (FDA) PAT initiative, PITs can be defined as the critical quality and performance attributes that have to be controlled during manufacturing of pharmaceutical products. Recently, Xu et al have concisely explained the concept and goals of the PAT framework and described applications of the process analytical technology for crystallization processes.[27]

Studies on the monitoring of the polymorphic transitions of theophylline and nitrofurantoin during the entire extrusion-spheronization pelletization process have not been reported previously. In the spirit of the PAT initiative, this article will assess the pseudopolymorphic changes in the APIs in question during all stages (blending, wet granulation, extrusion, spheronization, and drying) of the extrusion-spheronization process. An at-line PAT approach is used to increase the understanding of the behavior of the formulations used and the APIs during pelletization. NIR is used to monitor the blending of the starting materials. Raman spectroscopy, NIR, and X-ray powder diffraction have been used in the characterization of polymorphic changes during the process.

MATERIALS AND METHODS

Two different model compositions (NF and TP) were studied. The compositions were determined through thorough preliminary studies with an aim to prepare pellets with a uniform size and shape distribution. The API in composition NF was nitrofurantoin (Sigma-Aldrich Chemie, Steinheim, Germany), and the API in composition TP was anhydrous theophylline (Ph Eur, Orion Pharma, Espoo, Finland). The amount of drug was 10% (wt/wt) in both compositions. In addition, 28.4% (wt/wt) lactose monohydrate (80 mol/L Pharmatose; DMV Pharma, Veghel, The Netherlands) and 61.6% (wt/wt) microcrystalline cellulose (MCC) (50 mol/L Emcocel; Penwest Pharmaceuticals, Nastola, Finland) were used. The batch size was 2000 g. Purified water was used as a granulation liquid. The amount of moisturizing liquid was 80% (wt/wt) of the dry powder mass.

Methods

Blending of Powder Masses

The drug and the diluents were dry-mixed in a double cone mixer. The homogeneity of the mix was confirmed using near-infrared (NIR) measurements with a Fourier-Transform (FT)-NIR spectrometer (Bomem MD-160 DX; Hartmann & Braun, Quebec, Quebec, Canada). The use of NIR to control the mixing has been reported by several authors.[28-30] First a calibration curve with 7 mixtures of different amounts (0% to 100%) of API was made. The mixing time was optimized with a sample batch. A NIR probe was used to measure 10 different representative points of the mixture between predetermined intervals (starting point, 1 turn, 3 turns, 1 minute, 2 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes). The NIR data from the blending measurements were analyzed with principal component analysis (PCA). Principal components were calculated from the second derivative NIR spectra using Simca software (version 8.0; Umetrics AB, Umeå, Sweden).

Pelletization

Pellets were manufactured by the continuous extrusion-spheronization technique (Nica M6L mixer/granulator; Nica E140 radial screen extruder; Nica S320 spheronizer; Nica System AB, Mölndal, Sweden). The premixed powder masses were wet in the mixer/granulator. The speed of the powder feeder was 35 rpm (1275 g/min), and the liquid pump rate was 170 rpm (1020 g/min). Size of the granule outlet was 15 mm, measured from the lower side of the gap. The extruder agitator speed was 45 rpm, the screen thickness was 1.2 mm, and the diameter of the dies were 1 mm. The friction plate speed in the spheronizer was 900 rpm. The extrudate was spheronized for 1 minute.

Sampling

Three replicate samples (5 g) were taken to glass vials and closed with a cap at the end of each processing stage (ie, blending, granulation, extrusion, spheronization, and drying).

Drying and Moisture Control of Pellets

Three replicate samples from both the NF and TP batches of pellets were dried, and the moisture content was measured with an infrared dryer (Sartorius MA100; Sartorius GmbH, Göttingen, Germany) using 3 temperature levels (60°C, 100°C, and 135°C). The samples were heated until the weight loss rate was <0.1% in 24 seconds.

X-ray Powder Diffractometry

The radiograph patterns of all samples were analyzed with an XRPD θ-θ diffractometer (Bruker AXS, Karlsruhe, Germany). The XRPD measurements were taken in symmetrical reflection mode with CuKα radiation (0.154 Å) using Göbel mirror bent-gradient multiplayer optics. The scattered intensities were measured using a scintillation counter. The angular range was from 5° to 40° (2θ), with 0.05° steps (measuring time was 1 s/step). All samples were measured in room temperature. The XRPD measurements were made approximately 5 to 10 minutes after sampling.

Near-Infrared Spectroscopy

NIR measurements of all samples were made with a Fourier-Transform (FT)-NIR spectrometer (Bomem MD-160 DX) using Bomem-GRAMS software (version 4.04; Galactic Industries Inc, Salem, NH) and Teflon as a reference (99% reflective Spectralon; Labsphere Inc, North Sutton, NH). The spectra were analyzed through glass vials containing the sample. The spectra were recorded within the range of 10 000 to 4000 cm^{-1} with a resolution of

8 cm^{-1}, and they were averaged over 32 scans. Second derivative transformations of absorbance (1/R) were calculated with MATLAB software (version 6.5; MathWorks Inc, Natick, MA) using 11-point Savitzky-Golay smoothing. The NIR measurements were made approximately 1 to 2 minutes after sampling.

Raman Spectroscopy

The Raman spectra were measured at-line with a CCD Raman spectrometer (CDI Raman 785-1024; Control Development, Inc, South Bend, IN) with a 785-nm NIR diode laser (Starbright, Torsana Laser Technologies A/S, Skodberg, Denmark). The spectra were recorded over a range of 2000 to 200 cm^{-1} using a 1-second integration time. Spectral intensities were normalized by the standard normal variant transformation using MATLAB software.

RESULTS AND DISCUSSION

Blending

According to the NIR measurements, the blending of the formulations was complete after approximately 5 minutes. No change in homogeneity was seen after 10 minutes of mixing. The principal component analysis plot (Figure 1) shows how the homogeneity of mix evolved for the NF formulation. This figure illustrates how the second derivative NIR spectra from the blending measurements reside on the plot while the mixing process proceeds. The first
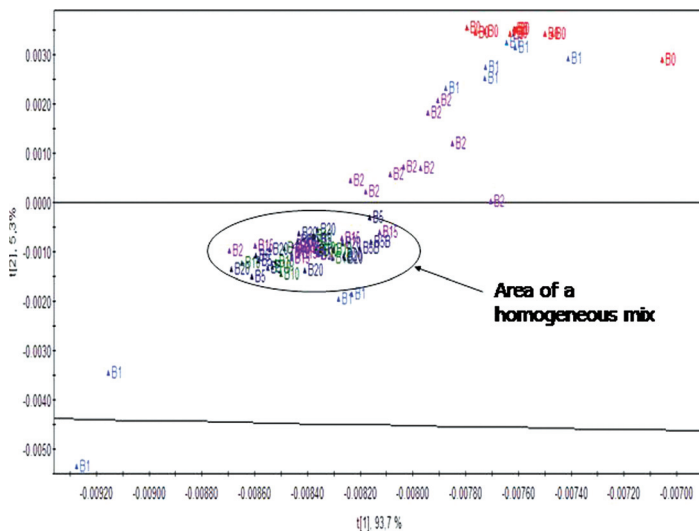

Figure 1. The PCA plot shows how the homogeneity of mix of the NF formulation evolved. Inhomogeneous measurement points with either high nitrofurantoin or high excipient rate are situated on the edges of the plot, farther away from the circle. The homogenous area is marked with the circle (B0, starting point; B1, 1 minute; B2, 2 minutes; B5, 5 minutes; B10, 10 minutes; B15, 15 minutes; B20, 20 minutes) (t1 = first principal component, t2 = second principal component).
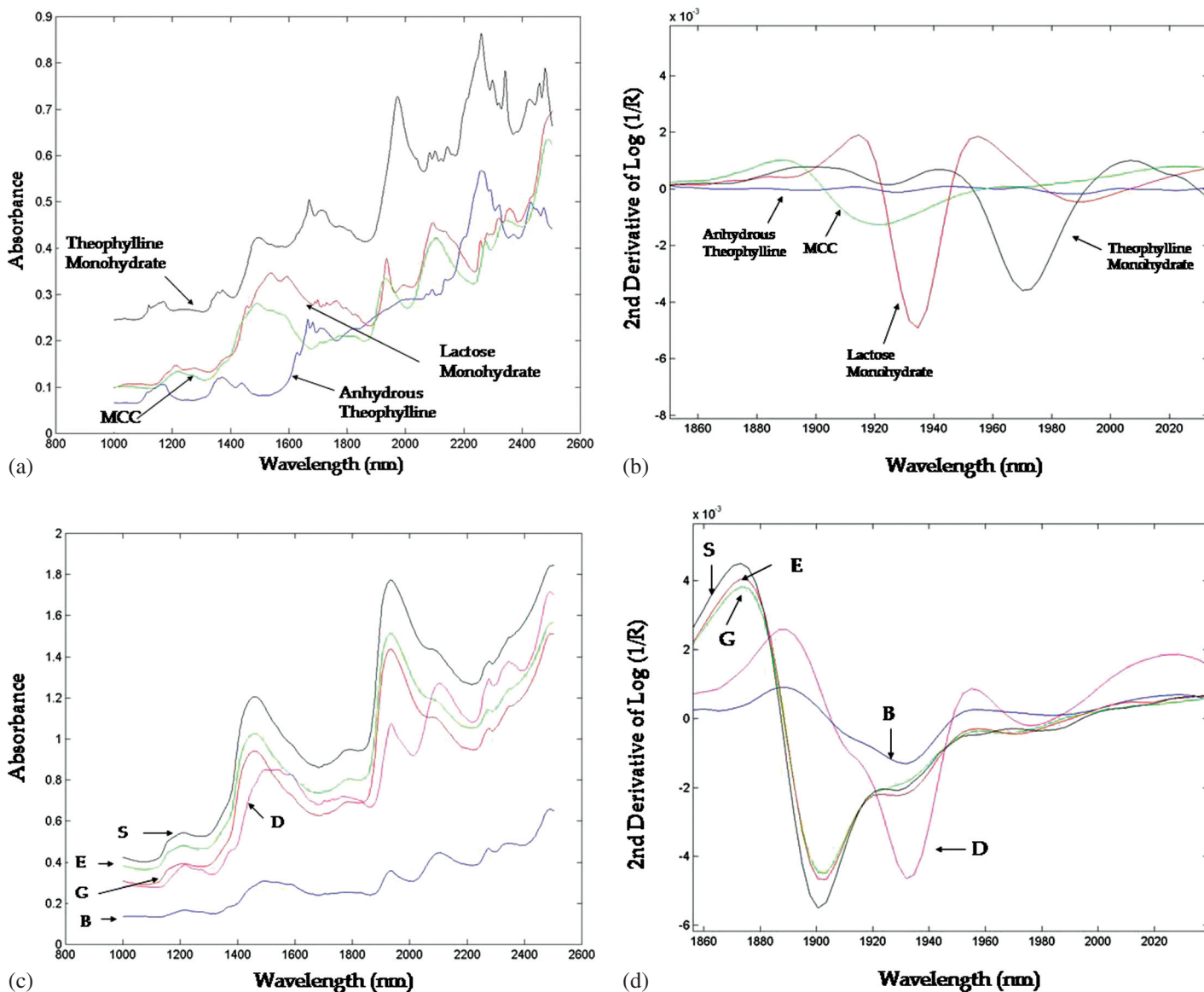
Figure 2. The NIR spectra for starting materials for formulation TP absorbance (a), for the second derivative for absorbance (b), and for the samples taken after different process steps (c) [blending (B), granulation (G), extrusion, spheronization (S), and drying (D)].

2 components explained 99.0% of the variation in data. Inhomogeneous measurement points, with either high nitrofurantoin or high excipient rate, are situated on the edge of the plot (B0 = starting point, B1 = 1 minute, B2 = 2 minutes, etc). The homogenous area is marked with a circle. The NIR-PCA method proved to be useful in determining the optimal blending time of a powder mixture.

Near-Infrared Spectroscopy

The NIR reflectance spectra are illustrated in Figures 2 and 3 (a–d). The spectra (absorbance and the second derivative for absorbance) for the starting materials for formulations TP and NF are shown in Figures 2 (a and b) and 3 (a and b), respectively. Figures 2 (c and d) and 3 (c and d) illustrate the NIR spectra for the samples taken after different proc-

ess steps: blending (B), granulation (G) (wetting), extrusion (E), spheronization (S), and drying (D).

The Theophylline Formulation

In the NIR region, absorption bands are caused primarily by overtones and combination vibrations of CH, NH, and OH groups. The most powerful absorption bands of pure water (OH stretching and bending vibrations) are situated at around 1450 and 1940 nm. NIR and water absorption has been described in preceding studies.[31-32] In this study, as expected, anhydrous theophylline did not have any absorption bands of OH at 1450 and 1940 nm (Figure 2, a and b). A reference spectrum for theophylline monohydrate was taken from a previous study. It shows 2 distinct absorption maxima at approximately 1475 and 1970 nm.
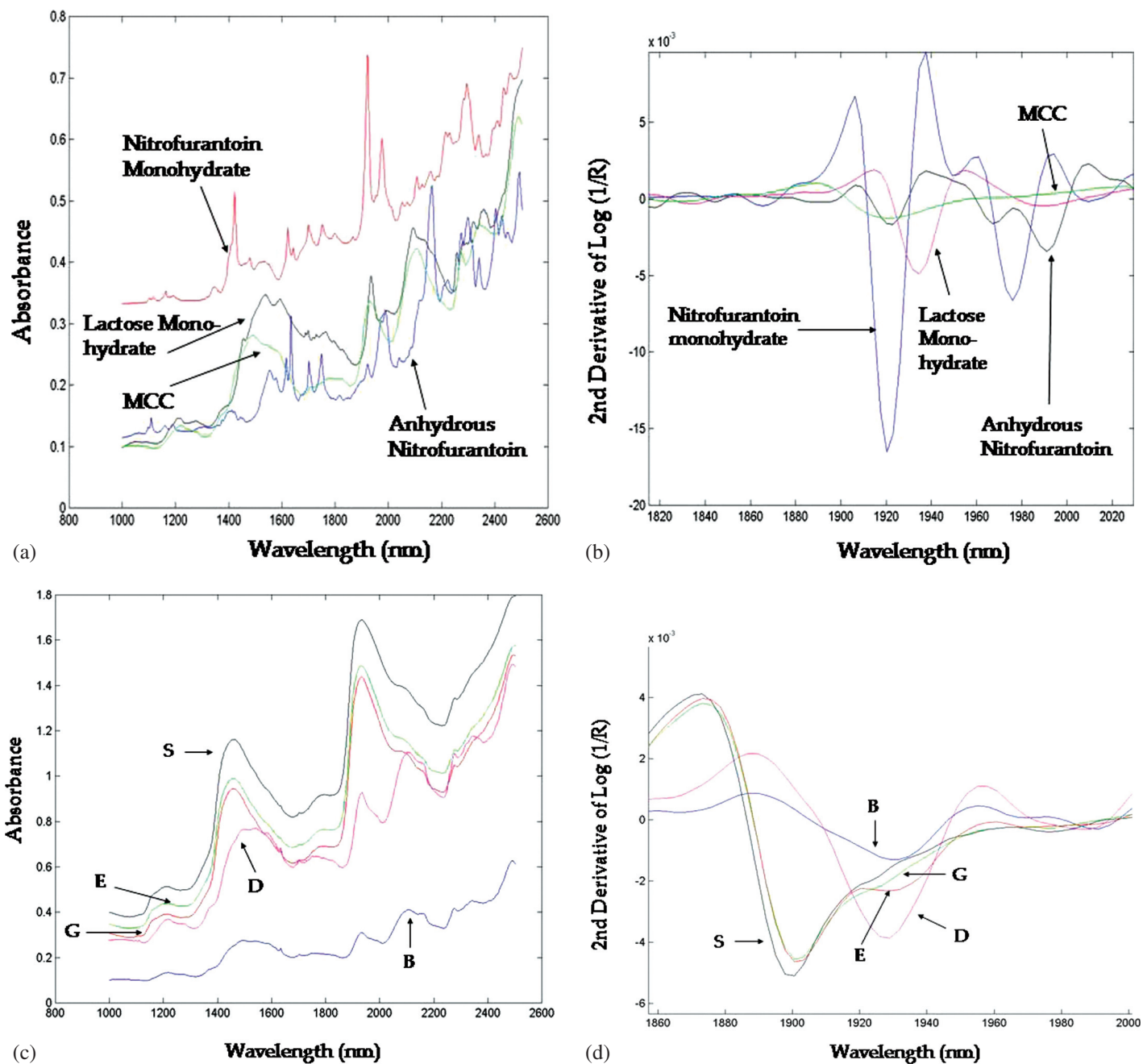
Figure 3. The NIR spectra for starting materials for formulation NF (a), for the second derivative for absorbance (b), and for the samples taken after different process steps (c) [blending (B), granulation (G), extrusion, spheronization (S), and drying (D)].

Next, we examined spectra for the different process stages for formulation TP (Figure 2, c and d). We noticed an increase in absorbance maxima when the process advances from granulation via extrusion to spheronization. However, the moisture content of the material in the spheronization step was slightly lower than after the granulation and extrusion steps (Table 1). The moisture content did not increase the spectral baseline. The increase in particle size has been shown to increase the baseline of spectra.[33-34] It seems that the relatively large rod-shaped extrudate does not increase the baseline as much as the smaller spheronized pellets. In Figure 2d (the second derivative of the absorbance of

TP), a typical spectra for anhydrous theophylline for the blended powder (TPB) is illustrated. For this batch and TPD, a distinct absorption maximum for lactose monohydrate was seen at 1933 nm.[35] At about 1970 nm, an absorption maximum for TPD (dried at 60°C) was detected, which indicates a pseudopolymorphic transformation to theophylline monohydrate. On the other hand, for the samples taken from the granulation, extrusion, and spheronization stages, an absorption maximum was discovered at approximately 1905 nm, which is distinctive for OH vibrations of free water molecules. No distinct water of crystalline theophylline could be detected at 1970 nm.

Table 1. Moisture Content (% wt/wt) of Nitrofurantoin (NF) and Theophylline (TP) Samples Measured with an Infrared Dryer ($n = 3$)*

	NF		TP	
	%	SD	%	SD
B	3.45	0.27	3.70	0.13
G	43.62	0.19	43.94	3.22
E	43.46	1.27	44.22	1.72
S	40.09	0.41	40.71	1.07
D	1.87	0.04	2.24	0.23

*B, blending; G, granulation; E, extrusion; S, spheronization; D, drying.

Consequently, the results indicate that polymorphic changes of theophylline cannot be detected using NIR spectral data because of the large amount of water in the system causing a saturation of the signal. This saturation prevents the detection of a possible monohydrate formation at 1933 nm. Räsänen et al[15] were able to detect a transformation of anhydrous theophylline to monohydrate using NIR spectroscopy in masses with lower moisture contents than those in this study. It has been reported that wet theophylline anhydrate was converted to monohydrate in the presence of MCC during pelletization using the extrusion-marumerizer technique.[10] In this study, the moisture content of samples TPG, TPE, and TPG was very high (~40%). It is, therefore, likely that a transformation has taken place and hydration has occurred. As expected, the XRPD measurements described below confirmed the pseudopolymorphic changes in the wet samples.

The Nitrofurantoin Formulation

The results for the NF composition are similar to those for the TP formulation. The NIR reflectance spectra for starting materials (Figure 3, a and b) show the 2 distinctive absorption maxima for nitrofurantoin monohydrate at approximately 1420 and 1975 nm. When examining the spectra for the different process stages for formulation NF, an increase in absorbance maxima in the steps NFG, NFE, and NFS at 1900 nm can be seen (Figure 3, c and d). The XRPD data indicate a hydrate formation of anhydrous nitrofurantoin. For NFB and NFD (dried at 60°C), no distinctive peaks of water were detected. This implies that during the process steps in which water is present a polymorph transformation takes place, but during drying, the monohydrate returns to an anhydrous form. However, XRPD and Raman results revealed that the hydrated form of nitrofurantoin is present for the NFD (dried at 60°C) sample. The NIR was not able to detect this due to a disturbance of overlapping signals from the excipients, especially lactose. Formulations with relatively low drug content can be difficult to study with NIR.

X-Ray Powder Diffraction

Figure 4a shows the distinct diffraction patterns for the excipients of formulations TP and NF. The XRPD diffraction patterns for the anhydrous and monohydrate forms of the APIs are presented in figure 4, b and c, together with diffraction patterns for the samples taken from the different process steps for both formulations.

The Theophylline Formulation

The use of characteristic XRPD patterns of anhydrous theophylline and theophylline monohydrate have been described thoroughly in the literature.[36-38] The XRPD patterns (Figure 4b) for formulation TP illustrate that after blending the dry powder has the distinct peak for anhydrous theophylline at 12.6° (2θ) and 7.1° (2θ). When the dry powder is moistened during granulation, distinct XRPD reflections for monohydrate occur at approximately 11.4° (2θ) and 14.7° (2θ). The small peak at 12.5° (2θ) is either a peak for lactose monohydrate or anhydrous theophylline. In the next processing stage (extrusion), distinct peaks for theophylline monohydrate were detected around 14.7° (2θ). The same holds for the spheronization stage. All wet samples seem very amorphous, especially the sample after spheronization, although distinct patterns of lactose monohydrate dominate. The diffraction patterns show characteristic peaks of both theophylline monohydrate and anhydrate at the 60°C drying temperature and peaks of anhydrate at the 100°C and 135°C drying temperatures. In contrast to the NIR results, the XRPD measurements show polymorphic changes in wet samples. This finding supports the expected polymorphic transformation from anhydrous theophylline to theophylline monohydrate during the extrusion-spheronization process. The drying process does not initiate a total retransformation of the monohydrate form to anhydrate at 60°C. This drying temperature is not high enough to discharge the hydrate, and the monohydrate remains within the hard core of the pellet.

The Nitrofurantoin Formulation

Characteristic XRPD patterns for anhydrous nitrofurantoin and its monohydrate have been clearly presented by Otsuka et al[23] The XRPD patterns for formulation NF in Figure 4c illustrate that after blending the dry powder has vague characteristic peaks for anhydrous nitrofurantoin at 14.4° (2θ) and 28.8° (2θ). The signals from excipients, mainly lactose, dominate and make interpretation somewhat difficult. A strong peak at 12.5° (2θ) could be the peak for lactose monohydrate or the nitrofurantoin monohydrate. When the dry powder was moistened during granulation, we observed peaks at 27.2° (2θ) and 28.8° (2θ), indicating that monohydrate and anhydrous form were present,
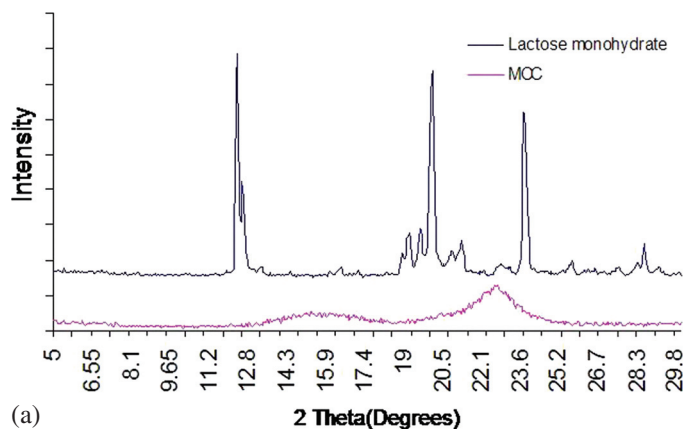
(a)
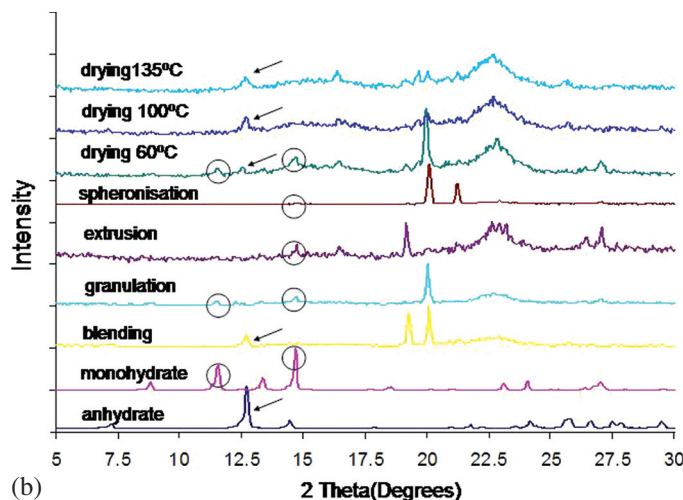
(b)
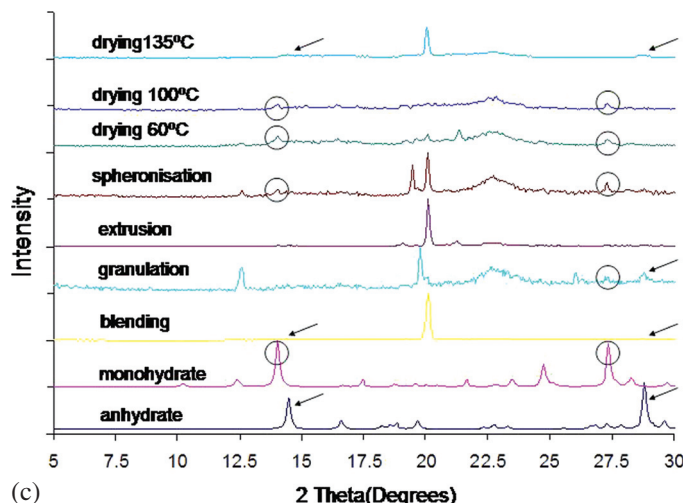
(c)

Figure 4. The distinct XRPD patterns for the excipients used in formulations TP and NF (a). The XRPD patterns for the different process steps for both formulations TP (b) and NF (c). Distinct peaks for anhydrate are shown with arrows, and distinct peaks for monohydrate are shown with circles. The reference diffraction patterns for theophylline and nitrofurantoin are shown at the bottom of parts b and c, respectively.

respectively. After the next process stage, extrusion, distinct peaks of either form were not really detected. After the spheronization stage, clear peaks of nitrofurantoin monohydrate were seen at 13.9° (2θ) and 27.2° (2θ). These

findings support the polymorphic transformation from anhydrous nitrofurantoin to nitrofurantoin monohydrate during the extrusion-spheronization process. In contrast to the NIR results, the XRPD measurements show polymorphic changes in the samples. The dried pellets seem very amorphous; however, a characteristic peak for nitrofurantoin monohydrate were again detected at 13.9° (2θ) and 27.2° (2θ) for samples dried at 60°C and 100°C. The dehydration occurs only in the highest temperature (135°C). This was seen in the diffraction pattern peaking at 14.4° (2θ) and 28.8° (2θ).

Raman Spectroscopy

Different Raman spectra are presented in Figure 5, a to d. Spectra for pure anhydrous APIs and their monohydrates are illustrated in Figure 5a, and some other cases from this study are shown in Figure 5, b to d.

The Theophylline Formulation

The Raman spectra for anhydrous theophylline and theophylline monohydrate have been described previously.[16,25,39] Since the amount of drug was relatively low, it was difficult to detect the hydrate formation from the Raman spectra measured at-line during processing. Previously, it had been shown that theophylline was a good Raman scatterer.[16,25,39] In these studies, however, the amount of drug compared with excipients had been rather large, more than 50% wt/wt. In our research, the amount of API in the formulation was 10% (wt/wt). This amount of excipients seemed to nullify the good Raman scattering ability of theophylline. Nevertheless, small characteristic changes in the C = O region at around 1700 to 1650 cm^{-1} were detected indicating hydrate formation after the water was added into the process. At these spectral regions, lactose and MCC had minor or no bands. Figure 5b shows the Raman spectra for the dried samples. The sample that had been dried at 60°C had a characteristic peak of anhydrous theophylline at ~1690 cm^{-1}, and the samples dried at higher temperatures lack this peak, indicating dehydration.

The Nitrofurantoin Formulation

Compared with theophylline, nitrofurantoin possessed better Raman scattering properties with the formulation used. In Figure 5c, the hydrate formation during processing could be seen. The spectra for the dry blend and sample taken after spheronization are shown. We recognized a distinct upshift in the spectra at several locations, eg at approximately 1430 cm^{-1}, 1500 cm^{-1}, and 1600 cm^{-1}, illustrating the formation of nitrofurantoin monohydrate. After examining the dried samples, we noticed that dehydration
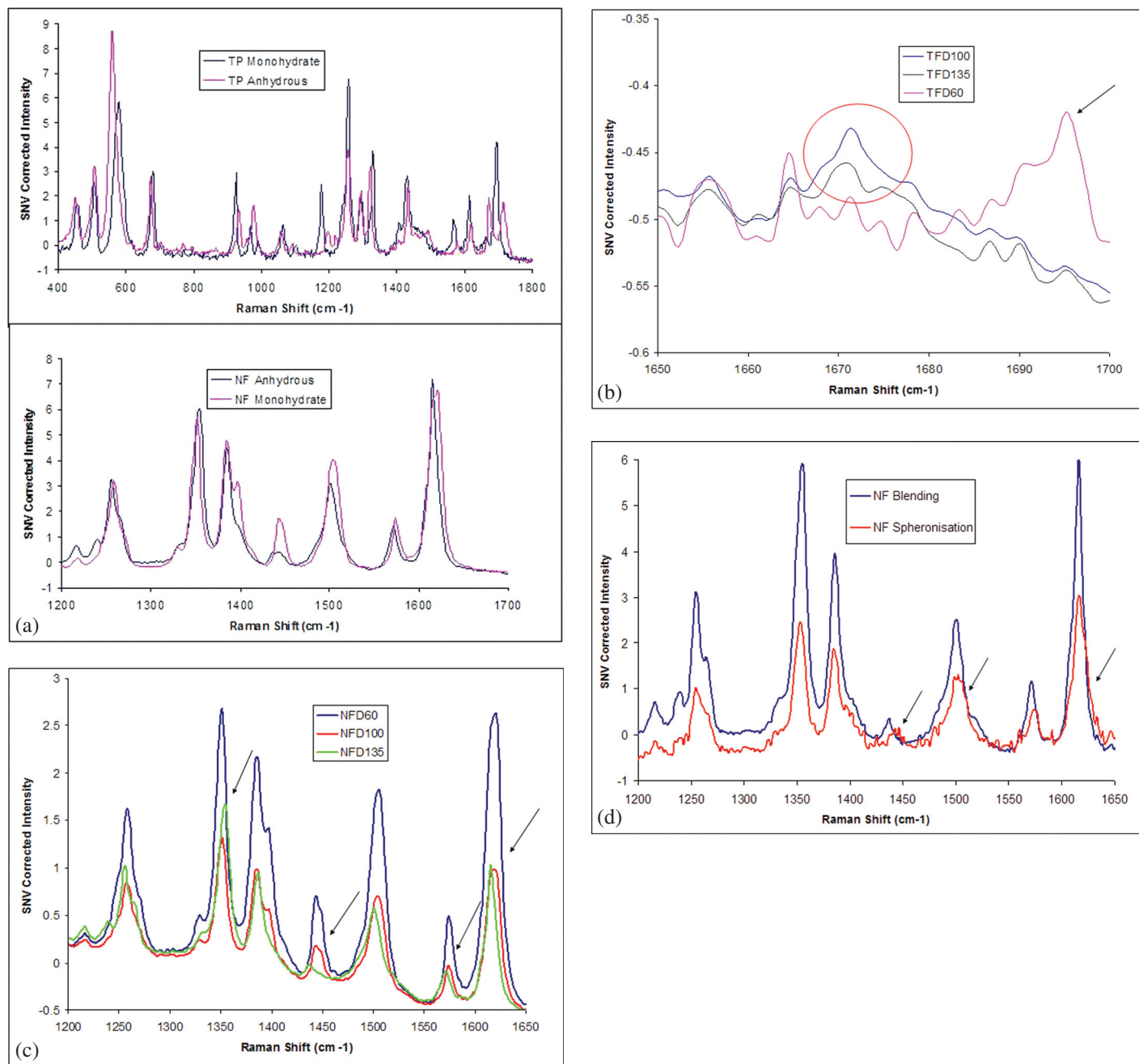
Figure 5. Raman spectra for pure anhydrous APIs and their monohydrates (a). Raman spectra for dried samples of formulation TP (the circle shows the distinct peaks for anhydrous theophylline) (b). Raman spectra for formulation NF showing the sample measured after the blending stage and after the spheronization stage (c). Raman spectra for the dried samples of formulation NF (d). Peaks where characteristic shifts happen are marked with arrows.

had occurred only in the highest temperature (135°C). The dehydration of the monohydrate in the Raman spectra were seen as clear downshifts at approximately 1430 cm^{-1}, 1500 cm^{-1}, and 1600 cm^{-1} and an upshift at approximately 1350 cm^{-1}.

General Observations

The hydrate formation kinetics and mechanisms for nitro-furantoin and theophylline during a wet-granulation proc-ess are different. With theophylline, water molecules form hydrates mainly through space filling, ie the water mole-cules organize themselves within the crystal lattices.[1] This phenomenon has not been reported with nitrofurantoin, and it is thought that the water is primarily absorbed on surfaces. Moreover, theophylline is more water-soluble (∼12 mg/mL) than nitrofurantoin (∼0.3 mg/mL), resulting in better wetting properties and, thus, easier hydrate forma-tion for theophylline. Consequently, this can affect the dry-ing mechanisms and the releasing and migration of water

from the pellets. When the water is within the structure of theophylline crystals, the drying is slower than that of the nitrofurantoin pellets. The drying temperature of 60°C was not enough to change the theophylline monohydrate to anhydrous theophylline. At 60°C and higher temperatures, the hydrate should transform to the anhydrous form relatively quickly.[3] The drying temperature had a significant effect on dehydration in both formulations. For a channel hydrate (theophylline), dehydration occurred at lower drying temperatures. In the case of isolated site hydrate (nitrofurantoin), dehydration was observed at higher temperatures.

The use of an at-line approach is applicable to monitor wet granulation-induced phase transformations of APIs. If we examine the approach from the perspective of the PAT initiative, it is obvious that for certain substances a key measure of end product quality can be the (pseudo)polymorphic state of the API. Therefore, tools to identify these changes are needed. Naturally, we also need the theoretical understanding of these possible transformations. For example, we can determine most critical process variables for the described extrusion-spheronization process: (1) blending time of starting materials, and (2) drying temperature of pellets. With inhomogeneous mixing, problems with content uniformity and the possibility of poor process performance due to improper wetting of the mix may occur. The relevance of the choice of drying temperature has been discussed earlier.

As the extrusion-spheronization pelletization process is continuous and relatively fast and involves relatively high amounts of water, real-time (on-line) detection of possible phase transitions of APIs would be advantageous. Nevertheless, at-line measurements gave an adequate amount of information to understand and monitor the pelletization process. In this study, the amount of drug in the formulations was lower than in real formulations of nitrofurantoin and theophylline. This would indicate that the difficulties of interpretations in overlapping signals of APIs and excipients would be less likely in normal practice with these drugs but could be a reality with other compounds. Nevertheless, this study shows that complementary techniques must be used when critical quality parameters for any given formulation are built.

CONCLUSIONS

NIR spectroscopy gave valuable real-time data about the state of water in the system, but it was not able to detect the hydrate formation in the theophylline and nitrofurantoin formulations during the granulation, extrusion, and spheronization stages because of the saturation of the water signal. XRPD and Raman spectroscopy were able to identify the pseudopolymorphic changes, but the strong signals

from the excipients complicated the interpretations. The mixing and drying phases were the most critical steps of the process. The at-line process analytical approach, using complementary techniques (NIR, Raman, and XRPD), proved helpful in gaining a wider understanding of the relatively fast process occurring in phase transformations of APIs. To reach an understanding of the process, complementary analytical techniques are absolutely necessary when signals from APIs and different excipients overlap each other.

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