Excipient Selection Can Significantly Affect Solid-State Phase Transformation in Formulation During Wet Granulation

Submitted: August 12, 2004; Accepted: April 19, 2005; Published: October 6, 2005

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ABSTRACT

Phase transformations in formulations can lead to instability in physicochemical, biopharmaceutical, and processing properties of products. The influences of formulation design on the optimal dosage forms should be specified. The aim here was to investigate whether excipients with different water sorption behavior affect hydrate formation of nitrofurantoin in wet masses. Nitrofurantoin anhydrate was used as a hydrate-forming model drug, and 4 excipients with different water-absorbing potential (amorphous low-substituted hydroxypropylcellulose, modified maize starch, partially amorphous silicified microcrystalline cellulose, and crystalline α-lactose monohydrate) were granulated with varying amounts of purified water. Off-line evaluation of wet masses containing nitrofurantoin anhydrate and excipient (1:1) was performed using an X-ray powder diffractometer (XRPD) and near-infrared spectroscopy, and drying phase was evaluated by variable temperature XRPD. Only amorphous excipient in the formulation retarded hydrate formation of an active pharmaceutical ingredient (API) at high water contents. Hygroscopic partially crystalline excipient hindered hydrate formation of API at low water contents. Crystalline excipient was unable to control hydrate formation of API. The character of excipient affects the stability of formulation. Thus, correct selection of excipients for the formulation can control processing-induced phase transitions and improve the storage stability of the final dosage form.

KEYWORDS: nitrofurantoin, near-infrared spectroscopy, sorption, X-ray powder diffraction

INTRODUCTION

Phase transformations in formulations can influence pharmaceutical and biopharmaceutical properties, such as physical stability, dissolution rate, and bioavailability, of the final dosage form. Physical form changes can occur at various stages of the formulation process, for example, during wet granulation, drying, and storage.[1,2] Thus, it is important to determine whether phase transformations occur, and, if so, what factors influence them. The impacts of formulation design on optimal dosage forms should be specified. The quality of dosage forms cannot be tested into final products; product quality and performance should be achieved and assured by the design of effective and efficient manufacturing processes.[3] The knowledge of processing options, process parameters, and material attributes can be gained by, for example, process analytical technologies (PAT). The approaches of PAT are based on science and engineering principles for evaluating and diminishing risks related to poor product and process quality.[4] Therefore, PAT should be utilized in pharmaceutical development, manufacturing processes, and quality control to improve the formulation design and process development and to minimize the process-induced phase transitions in formulation.[3,5]

A pharmaceutical dosage form generally consists of a drug combined with a varying number of excipients that have been added to the formulation to facilitate its preparation and function as a drug delivery system. Although excipients are considered to be inert in therapeutic or biological actions, they should hinder unwanted phase transitions and ensure the required stability of the drug in the formulation during the manufacturing process and storage. However, each drug or excipient and, thus, each formulation, has a different affinity for moisture. Because moisture sorption by amorphous and crystalline materials is usually quite different, this can be used to distinguish between them.[6,7] Crystalline materials typically adsorb moisture at their surfaces in small quantities or form hydrates in larger quantities. Water can interact with crystalline solids by adsorption of moisture on particle surfaces, crystal hydrate formation, deliquescence, and capillary condensation.[6] In contrast, amorphous materials absorb vapors in relatively large amounts; when moisture is absorbed, the bulk properties of the solid can be significantly altered. Moisture sorption/desorption isotherms describe interactions between

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moisture and solid materials. They link the total water content of a material to the relative humidity in which the material is treated[8] and are among the most commonly used terms for determining the quantitative relationship between solids and moisture.[9]

The crystalline unsolvated drug will likely form a hydrate during wet granulation, but the hydrate formed could also convert to another unexpected form on drying.[10-12] Both the active pharmaceutical ingredients (APIs) and excipients in the solid-dosage form may exist in crystalline forms, such as α-lactose monohydrate (LMH), or may be amorphous. Amorphous character is common in the polymeric molecules used as excipients. The presence of small amounts of amorphous material can affect the interaction between the powder and other components of a formulation and can, therefore, influence the physical and chemical stability of a product.[13] Excipients used in this study have different water sorption properties: pregelatinized starch and low-substituted hydroxypropylcellulose (L-HPC) were selected as amorphous excipients, and silicified microcrystalline cellulose (SMCC) was selected as a partially amorphous excipient. The effect of an excipient depends on the amount present and, hence, the amount of moisture it brings into the drug-excipient interaction, as well as the relative ability of each solid to take up and retain water at a particular temperature and relative humidity.[6,14] The quantity of water adsorbed by crystalline solids depends on the polarity of the surface and the specific surface area of the crystalline material[15] and, hence, the particle size of the material. In contrast to crystalline solids, water uptake by amorphous solids is determined by the total mass of the amorphous material, which does not depend on its specific surface area. Amorphous material can absorb a large quantity of water while the free volume increases; water acts as a plasticizer and reduces the glass transition temperature.[16]

Polymorphism and pseudopolymorphism of nitrofurantoin have been reported by Pienaar et al[17,18] and Caira et al,[19] and nitrofurantoin has been found in 4 modifications of nitrofurantoin: anhydrous forms, designated α and β, and monohydrous forms, designated I and II. Phase transformations of nitrofurantoin anhydrate with 2 excipients under high-humidity conditions were reported earlier by Otsuka and Matsuda[20] Phase transitions in nitrofurantoin formulations may take place during storage under adverse conditions of temperature and humidity, as well as during a variety of processing conditions. Excipients are, therefore, important components of pharmaceutical formulations, and they can participate actively in improving the characteristics of formulations.

The aim of preformulation is to design a quality product and the manufacturing process to provide the product in a reproducible manner.[4] When designing formulations, it is important to know which crystal form of a drug is present at the various stages of a process and after the product is stored in its final form. At the very least, how changes in the crystal form might affect performance or stability of the drug product should be known. Crystalline nitrofurantoin monohydrate, for instance, is stable in high humidity but is disrupted by mechanical stress, such as grinding, and transformed into a noncrystalline solid in low humidity.[21] On the other hand, aqueous solubility of the anhydrate is greater than that of its hydrate form at temperatures at which the hydrate crystallizes from water.[22] The aim of this study was to investigate whether crystalline or amorphous excipients with different water sorption properties affect hydrate formation of nitrofurantoin in wet masses. Nitrofurantoin anhydrate was used as a hydrate-forming model drug, and 4 excipients with different water-absorbing potential (amorphous L-HPC [LH-21], modified starch, partially amorphous SMCC, and crystalline LMH) were granulated with varying amounts of purified water. Off-line evaluation of wet masses containing nitrofurantoin anhydrate and excipient (1:1) was performed using an X-ray powder diffractometer (XRPD) as a basic technique and near-infrared (NIR) spectroscopy as a PAT tool. To compare the dehydration behavior of 4 different wet formulations and evaluate solid-state properties during drying, the drying process was conducted with a variable temperature (VT)-XRPD under ambient conditions.

MATERIALS AND METHODS

Materials

The 4 different excipients used are presented in Table 1. Nitrofurantoin anhydrate (Sigma-Aldrich Chemie, Steinheim, Germany) was selected as a hydrate-forming model drug. To obtain a reference hydrate, nitrofurantoin anhydrate was dissolved in purified water at 60°C. Needle-like monohydrate crystals were obtained by slow cooling of the solution. Crystal structures were verified by measuring the X-ray powder diffraction pattern of each model compound using the equipment described below and comparing with the structures from the Cambridge Structural Database (Cambridge Crystallographic Data Centre, Cambridge, UK). Measured patterns were compared with the calculated patterns generated using Mercury 1.2.1 (Cambridge Crystallographic Data Centre). The volume particle size distribution (Table 1) was determined by a method based on laser light diffraction (Laser Diffraction Particle Size Analyser LS13 320, Beckman Coulter Inc, Miami, FL). Specific surface area (Table 1) was measured using the nitrogen adsorption technique (TriStar 3000, Micromeritics Inc, Norcross, GA) based on the Brunauer-Emmett-Teller's (BET) adsorption theory.

Table 1. Physical Properties of Excipients Used in the Study: Excipients and Nitrofurantoin Anhydrate (1:1) Granulated With Different Amounts of Water

Excipient (Model, Brand Name, Company)	Average Particle Size (μm)	Specific Surface Area (m^2/g)	Amount of Water (g/g) Added to Dry Materials
L-hydroxypropylcellulose (grade LH-21; Shin-Etsu Chemicals Co Ltd, Tokyo, Japan)	54	0.97	0.1, 0.2, 0.3, 0.5, 0.7, 0.8, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5
α-Lactose monohydrate (Pharmatose 200M; DMV International, Veghel, The Netherlands)	43	0.52	0.1, 0.2, 0.3, 0.4
Starch, pregelatinized (Sta-rx 1500; Colorcon, Indianapolis, IN)	72	0.26*	0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 1.0, 1.5
Silicified microcrystalline cellulose (Prosolv 50; Penwest Pharmaceuticals, Nastola, Finland)	56	5.63	0.1, 0.2, 0.3, 0.5, 0.8

*Handbook of Pharmaceutical Excipients.[30]

Preparation of Wet Masses Containing Nitrofurantoin

Nitrofurantoin anhydrate and 4 different excipients were granulated with varying amounts of purified water (Table 1). The granulations were performed with a mortar and pestle to simulate the early stages of preformulation, when the amount of a new API is relatively small. Each excipient was mixed with nitrofurantoin anhydrate to make a dry binary powder mixture (1:1), after which water was added. The wet masses were stirred thoroughly and packed in tightly sealed plastic bags until analysis. The wet masses were studied on the first day and also on the second day after an overnight equilibration in plastic bags at room temperature.

Water Sorption

Samples containing nitrofurantoin anhydrate and excipients (1:1) were dried on trays at 45°C and 70 to 75 mbar for 24 to 48 hours in a vacutherm (Heraeus VT 6025, Kendro Laboratory Products GmbH, Hanau, Germany) and then dried additionally at 22°C in a vacuum desiccator (Nalgene Desiccator, Nalge Nunc International, Rochester, NY) at a relative humidity (RH) of 0% for 5 days. Moisture sorption properties of samples (approximately 500 mg) were determined gravimetrically before and after storage at 22°C under conditions of different RHs (0% to 95% RH). The different RH conditions were achieved in vacuum desiccators by using saturated salt solutions. Samples in triplicate in open glass vials were allowed to equilibrate in the vacuum desiccator and were stored for 1 and 2 weeks.

X-ray Powder Diffractometry

X-ray diffraction patterns were measured using a XRPD θ-θ diffractometer (Bruker axs D8, Bruker AXC GmbH, Karlsruhe, Germany). The XRPD experiments were performed in symmetrical reflection mode with CuKα radiation (1.54 Å) using Göbel Mirror bent gradient multilayer optics. The scattered intensities were measured with a scintillation counter. The angular range was 11 to 18°, with increments of 0.05°, and the measuring time was 1 s/step (3° 2θ/min). The angular range of 11 to 18° was used to quickly identify the samples in such a range, where the samples did not have the same reflections. The sorption samples were measured at room temperature after 2 weeks of storage under conditions of different RHs (0% to 95% RH).

The samples of drying experiments were measured using a VT-XRPD θ-θ diffractometer (Bruker axs D8, Bruker AXC GmbH). The wet masses at the highest water contents of each formulation were placed into the holder of an XRPD. The wet masses containing nitrofurantoin anhydrate and excipients (1:1) were heated with increments of 10°C from 25 to 270°C and maintained at the target temperature for 15 minutes. The heating rate was 0.2°C/s. The angular range was 5 to 40°, with increments of 0.1°, and the measuring time was 1 s/step (3° 2θ/min). The variable temperature diffraction patterns of the wet masses were measured 24 hours after water addition to ensure hydrate formation of nitrofurantoin. This method enabled following the phase transformations from nitrofurantoin monohydrate to anhydrate in excipient mixtures during the drying process.

XRPD Data Analysis

The estimation of the relative amount of nitrofurantoin monohydrate in the sample was based on the assumption that the experimental intensity curve is a linear combination of intensities of nitrofurantoin monohydrate and nitrofurantoin anhydrate. The structures of nitrofurantoin anhydrate and nitrofurantoin monohydrate in nitrofurantoin formulations were estimated by fitting the diffraction curves of both to the experimental diffraction curve of each sample. The amount of the 2 nitrofurantoin components in each sample was calculated as the ratio of the integrals of the intensities of the references (nitrofurantoin anhydrate and monohydrate) to the studied sample. Accuracy of this method is ±0.1.

NIR Spectroscopy

Off-line NIR spectra were measured with a Fourier Transform NIR spectrometer (Bomem MD-160 DX, Hartmann Braun, Quebec, Montreal, Canada) using Bomem-GRAMS software (v. 4.04, Galactic Industries Inc, Salem, NH) and Teflon as a reference (99% reflective Spectralon, Labsphere Inc, North Sutton, NH). The spectra were measured through the bottom of a glass vial containing the sample. The measurements were conducted in triplicate. Spectra were recorded over a range of 10,000 to 4,000 cm^{-1}, with a resolution of 16 cm^{-1}, and were averaged over 32 scans. Second derivative transformations of absorbance, log (1/R), were performed with 11-point Savitzky-Golay smoothing[23] using Matlab software (v. 5.3, MathWorks Inc, Natick, MA).

RESULTS

Characterization of Starting Materials

Characteristic X-ray diffraction patterns and NIR spectra of nitrofurantoin anhydrate and monohydrate and 4 different excipients (L-HPC [LH-21], modified starch, SMCC, and LMH), were observed using X-ray diffractometry in the angular range of 11 to 18° 2θ (Figure 1A) and by NIR spectrometry, focusing specifically on the first overtone water band at around 1,900 nm (Figure 1B).

XRPD Patterns of Starting Materials

Figure 1A presents the X-ray diffraction patterns measured for the starting materials. The reflections of the diffraction pattern of nitrofurantoin anhydrate were observed at 14.4° and 16.5° 2θ in the used angular range of 11 to 18° 2θ, consistent with previous findings.[19,24] The diffraction pattern of the nitrofurantoin anhydrate used here agreed with an earlier monoclinic β-polymorph of nitrofurantoin anhydrate,[19] where a is 7.840 Å, b is 6.486 Å, c is 18.911 Å, and β is 93.17°.[18] The diffraction pattern of the prepared nitrofurantoin monohydrate agreed with one previously described for orthorhombic nitrofurantoin monohydrate II, where a is 12.642 Å, b is 9.857 Å, c is 17.383 Å, and β is 90°.[17] The reflections of the diffraction pattern of nitrofurantoin monohydrate observed at 12.3, 13.9, and 17.3° in the angular range of 11 to 18° 2θ were consistent with previous findings.[19,24] A comparison of different powder patterns of nitrofurantoin forms are shown in Figure 1A.

The diffraction patterns of LMH and nitrofurantoin anhydrate included a reflection at about 16.5° 2θ in the same position, and, thus, it was not possible to use this for their characterization in the formulation. Wide reflections of the characteristic diffraction pattern of SMCC were observed at 12 to 18° 2θ. The diffraction patterns of L-HPC and starch were distinct in the angular range of 11 to 18° 2θ.

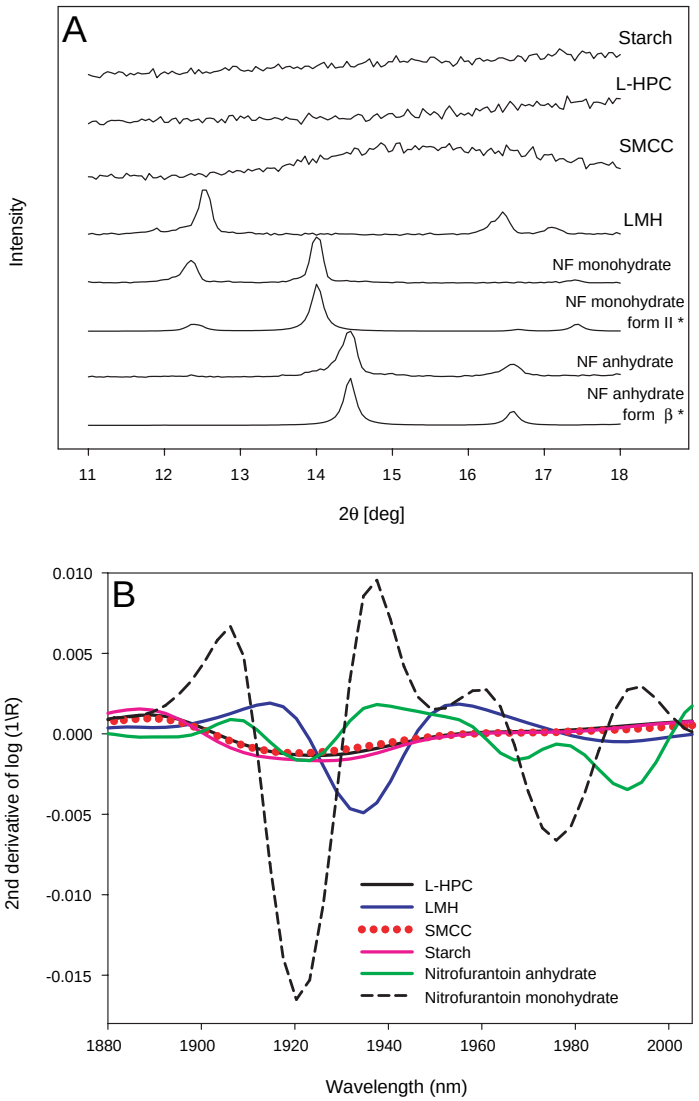

Figure 1. (A) Powder X-ray diffraction patterns of nitrofurantoin anhydrate (NF anhydrate), nitrofurantoin monohydrate (NF monohydrate) and studied excipients: LMH, SMCC, L-HPC (grade LH-21), and modified starch in the angular range of 11 to 18° 2θ. * indicates calculated XRPD patterns of nitrofurantoin anhydrate (NF anhydrate form β) and nitrofurantoin monohydrate (NF monohydrate form II), shown as controls. (B) NIR reflectance spectra of 4 excipients and spectra of nitrofurantoin anhydrate and monohydrate as controls. The second derivative of absorbance, log (1/R), at 1,880 to 2,005 nm. Characteristic peaks of nitrofurantoin monohydrate are shown at 1,920 and 1,975 nm.

NIR Spectra of Starting Materials

Distinct absorption maxima of water were identified in the 1,900 to 2,000 nm region depending on the material (Figure 1B). For nitrofurantoin, the water of crystallization was seen as an absorption maximum at 1,920 nm. Another absorption maximum for nitrofurantoin monohydrate was seen at 1,975 nm. For LMH, a distinct absorption maximum of water of crystallization was seen at 1,933 nm. The rest of the excipients had only minor absorption maxima at

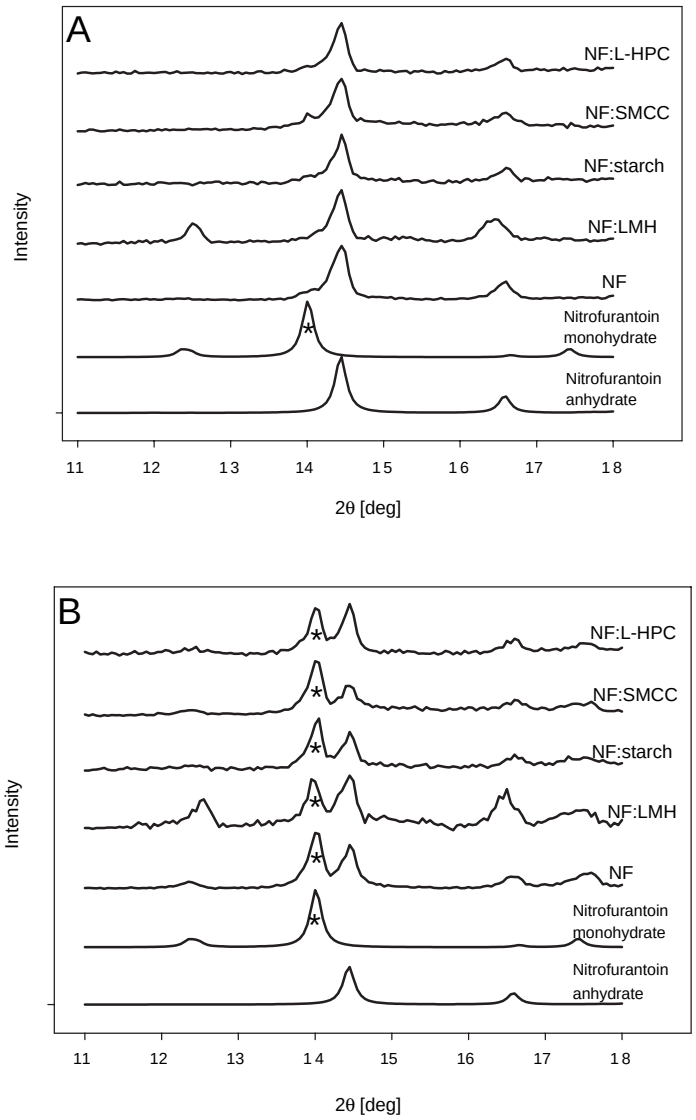

Figure 2. Powder X-ray diffraction patterns of formulations after storage at 85% RH (A) and at 95% RH (B) for 2 weeks. Calculated patterns of nitrofurantoin anhydrate and nitrofurantoin monohydrate are shown as controls. Formulations containing nitrofurantoin anhydrate (NF), NF:LMH, NF:starch, NF:SMCC, and NF:L-HPC. * indicates characteristic peaks of nitrofurantoin monohydrate.

range of 1,920 nm or 1,975 nm, which were not affecting identification.

Effect of Formulation on Water Sorption

The effect of humidity on formulations of nitrofurantoin anhydrate and 4 excipients (L-HPC [LH-21], modified starch, SMCC, and LMH), was investigated over a 2-week period. The formulations showed no difference after storage at 0, 11, 23, 33, 43, 52, 58 and 75% RH. However, at 85% RH, some features of nitrofurantoin monohydrate were present in the diffraction pattern of the formulation containing LMH and SMCC with nitrofurantoin anhydrate (Figure 2A). At a RH of 95%, all 4 of the formulations included features of diffraction patterns of anhydrous nitrofurantoin and nitrofurantoin monohydrate (Figure 2B). This transition could also be identified with the pure anhydrous nitrofurantoin stored under the same conditions.

The hydrate formation was also followed by NIR spectroscopy. The same water bands at 1,900 to 2,000 nm were identified by from the sorption samples (Figure 3). The transition of anhydrous nitrofurantoin to monohydrate was seen in the increasing absorption maxima at 1,920 and 1,975 nm. The hydrate formation of nitrofurantoin in all 4 of the formulations, including pure anhydrous nitrofurantoin, was observed at a RH of 95% (Figure 3B) but not at a RH of 85% (Figure 3A).

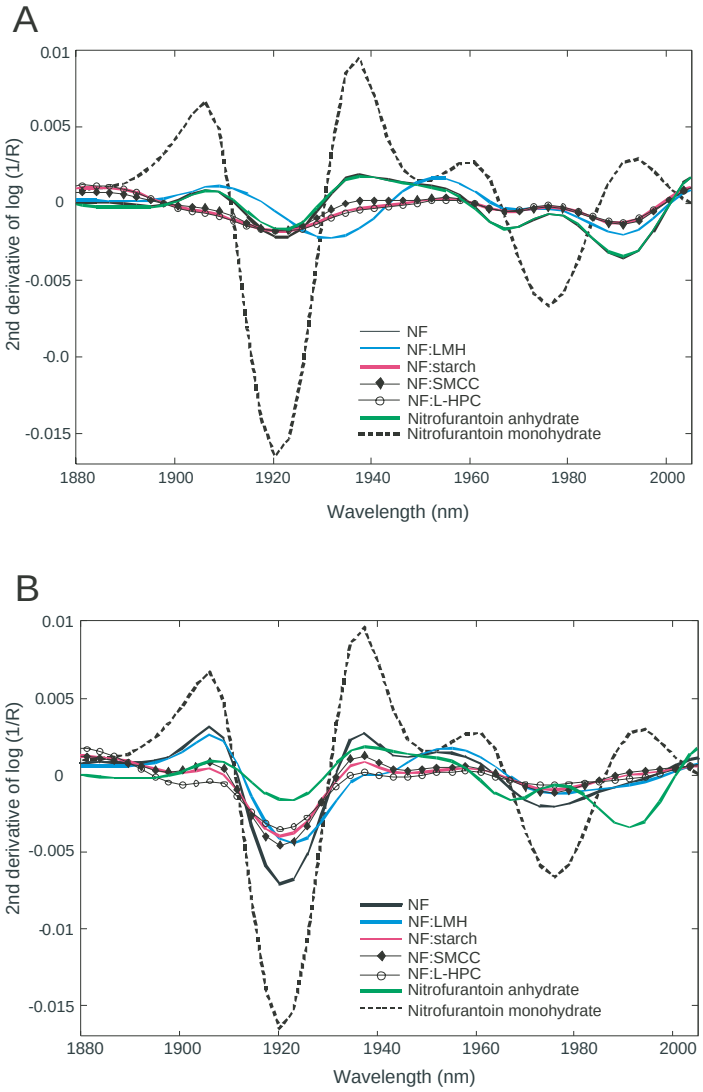

Figure 3. NIR reflectance spectra of formulations after storage at 85% RH (A) and at 95% RH (B) for 2 weeks. The second derivative of absorbance, log (1/R), at 1,880 to 2,005 nm. Formulations containing nitrofurantoin anhydrate (NF), NF:LMH, NF:starch, NF:SMCC, and NF:L-HPC. Nitrofurantoin anhydrate and nitrofurantoin monohydrate are shown as controls. Characteristic peaks of nitrofurantoin monohydrate are shown at 1,920 and 1,975 nm.

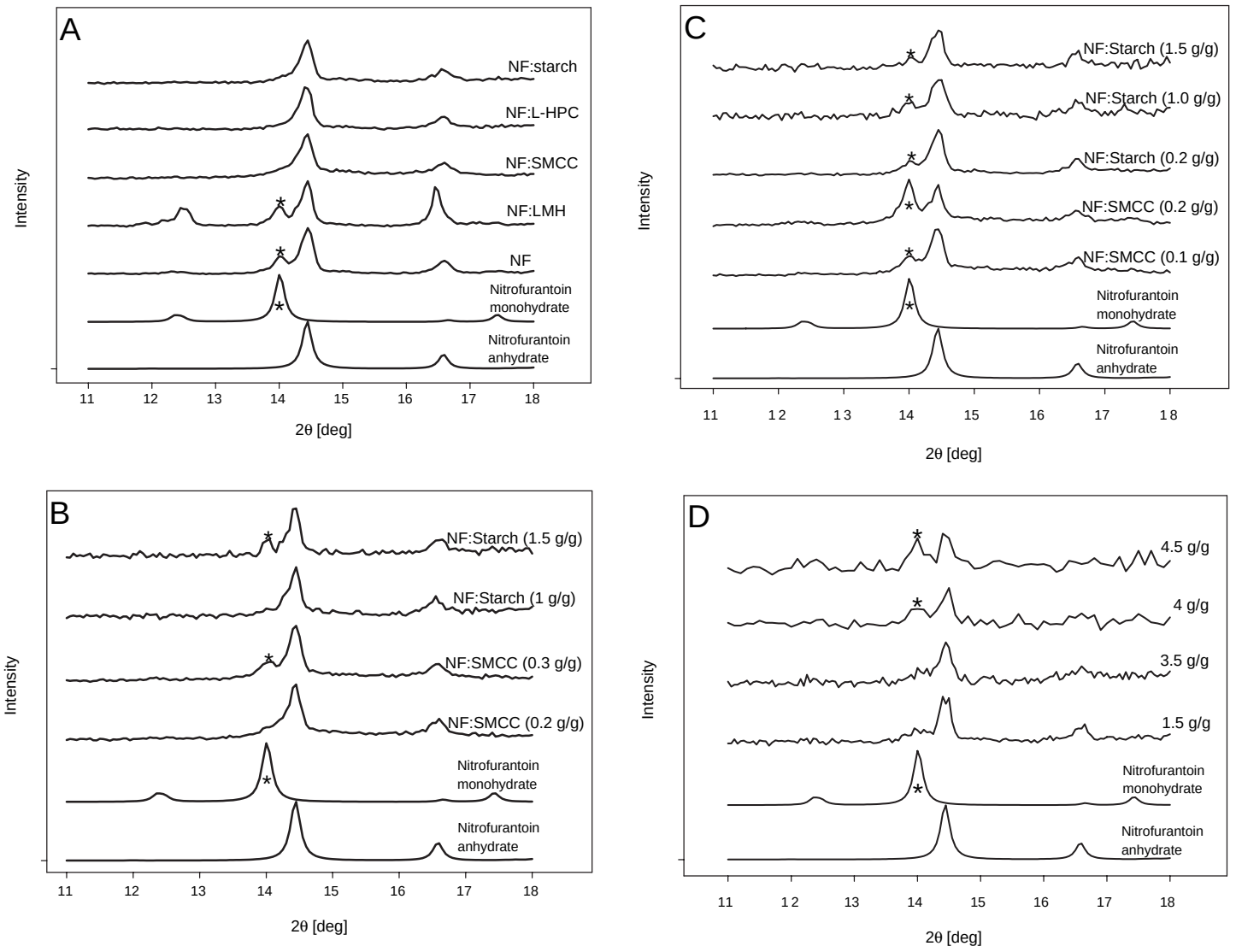

Figure 4. (A) XRPD patterns of nitrofurantoin wet masses after water addition of 0.1 g/g into the formulation on the first day. Formulations with nitrofurantoin anhydrate (NF):LMH, NF:SMCC, NF:L-HPC, and NF:starch measured in the angular range of 11 to 18°2θ. (B) XRPD patterns of nitrofurantoin wet masses after different water additions into the formulation on the first day. Formulations with SMCC (water additions of 0.2 or 0.3 g/g) and starch (water additions of 1 or 1.5 g/g) measured in the angular range of 11 to 18° 2θ. (C) XRPD patterns of nitrofurantoin wet masses after different water additions into the formulation on the second day. Formulations with SMCC (water additions of 0.1 or 0.2 g/g) and starch (water additions of 0.2, 1, or 1.5 g/g) measured in the angular range of 11 to 18°2θ. (D) XRPD patterns of nitrofurantoin wet masses containing L-HPC (1:1) on the second day. Water additions of 1.5, 3.5, 4, or 4.5 g/g into the formulation measured in the angular range of 11 to 18° 2θ.

Calculated patterns of nitrofurantoin anhydrate and nitrofurantoin monohydrate are shown as controls. *refers to characteristic patterns of nitrofurantoin monohydrate.

Solid-State Phase Transformations in Wet Masses

Solid-Water Interaction of Formulation Containing Only Model Drug

Nitrofurantoin anhydrate transformed completely to monohydrate with the addition of water to the formulation, as expected. The change began after the first (0.1 g/g) addition of water on the first day (Figure 4A). The features of nitrofurantoin monohydrate increased as a function of the amount of water in the wet masses, but the diffraction curve after water addition of 0.3 g/g on the first day still included features of both anhydrous nitrofurantoin and nitrofurantoin monohydrate. The wet masses were also studied after an overnight equilibration, and the transition of anhydrous nitrofurantoin to monohydrate was completed already after the first water addition of 0.1 g/g.

The water bands for the wet masses were identified by NIR (Figure 5A). The water related to the pseudopolymorphic transition of anhydrous nitrofurantoin was seen as an increasing absorption maximum at 1,920 nm. Another increasing absorption maximum of nitrofurantoin monohy-

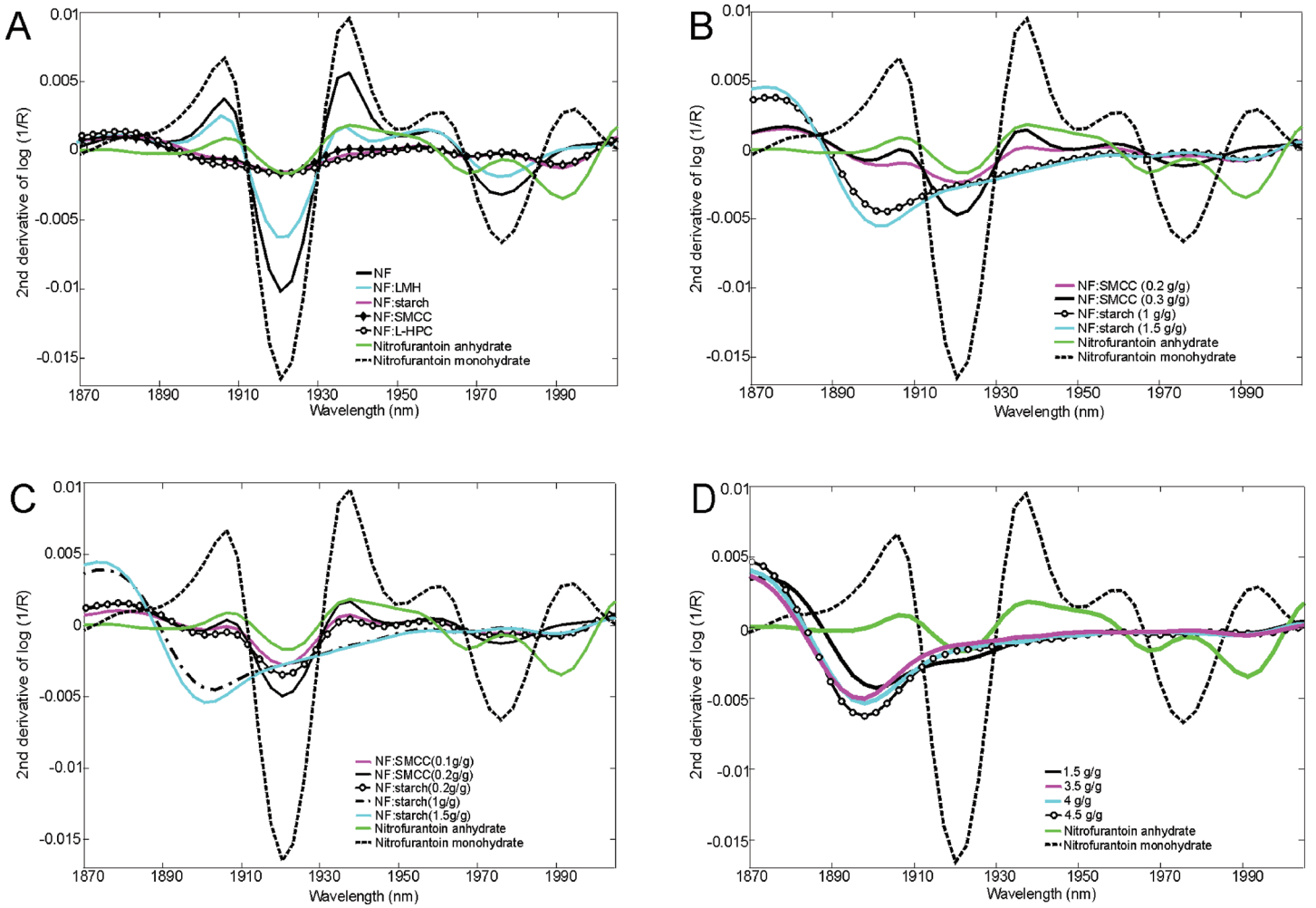

Figure 5. (A) Second-derivative NIR spectra of nitrofurantoin wet masses after water addition of 0.1 g/g into the formulation on the first day. Formulations (1:1) containing nitrofurantoin anhydrate (NF):LMH, NF:SMCC, NF:L-HPC, and NF:starch. The second derivative of absorbance, log (1/R), at 1,870 to 2,005 nm. Characteristic peaks of nitrofurantoin monohydrate are shown at 1,920 and 1,975 nm. (B) Second-derivative NIR spectra of nitrofurantoin wet masses after different water additions into the formulation on the first day. Formulations (1:1) containing SMCC (water additions of 0.2 or 0.3 g/g) and starch (water additions of 1 or 1.5 g/g) at 1,870 to 2,005 nm. (C) Second-derivative NIR spectra of nitrofurantoin wet masses after different water additions into the formulation on the second day at 1,870 to 2,005 nm. Formulations containing SMCC (water additions of 0.1 or 0.2 g/g) or starch (water additions of 0.2, 1 or 1.5 g/g). (D) Second-derivative NIR spectra of nitrofurantoin wet masses containing L-HPC (1:1) on the second day at 1,870 to 2,005 nm. Water additions of 1.5, 3.5, 4, or 4.5 g/g into the formulation.

Nitrofurantoin anhydrate and nitrofurantoin monohydrate are shown as controls. Free water was seen at an absorption maximum of around 1,900 nm.

drate was seen at 1,975 nm. After 0.1 g/g of water was added to the formulation, the pseudopolymorphic transition of anhydrous nitrofurantoin was not yet completed, as seen in Figure 5A. After an overnight equilibration, the transition of anhydrous nitrofurantoin to monohydrate was completed after the first 0.1 g/g addition of water, consistent with XRPD data.

Solid-Water Interaction of Formulation Containing Crystalline Excipient

Pseudopolymorphic changes of nitrofurantoin anhydrate in the formulations containing excipients with crystal structure began after the first (0.1 g/g) addition of water to the formulation (Figure 4A). LMH with minimal water-absorbing potential was unable to control the hydrate formation of nitrofurantoin. The diffraction patterns of this formulation included features of both anhydrous nitrofurantoin and nitrofurantoin monohydrate. The features of nitrofurantoin monohydrate increased as a function of the amount of water, as expected. This was also confirmed by NIR spectroscopic methods. The transformation was seen as an increasing absorption maximum at 1,920 and 1,975 nm after the first addition of water to the formulation (Figure 5A). After an overnight equilibration, the transition of anhydrous nitrofurantoin to monohydrate was not yet completed.

Solid-Water Interaction of Formulation Containing Partially Crystalline Excipient

Hygroscopic cellulose SMCC was able to hinder the formation of nitrofurantoin monohydrate at low water contents (Figure 4B and 5B), consistent with previous findings.[25] On the first day, nitrofurantoin monohydrate began to transform after the addition of 0.3 g/g of water (Figure 4B), but the wet masses still had anhydrate left after a water addition of 0.5 g/g. Nitrofurantoin monohydrate alone was seen in the formulation with a water content of 0.8 g/g.

Similar results were observed by NIR. The water bands for the wet masses showed that nitrofurantoin anhydrate started to transform to monohydrate in the SMCC formulation, with a water content of 0.3 g/g (Figure 5B). After a water addition of 0.5 g/g, the wet masses had water bands for nitrofurantoin monohydrate and free water. Free water was observed to have a gradually increasing absorption maximum at around 1,900 nm.[26] After water addition of 0.8 g/g, pseudopolymorphic transition of anhydrous nitrofurantoin was completed, and the added water continued to have an absorption maximum at around 1,900 nm.

The wet masses were also studied after an overnight equilibration. On the second day, the transformation with the SMCC formulation was seen already after the first water addition of 0.1 g/g (Figure 4C), but features of both anhydrous nitrofurantoin and nitrofurantoin monohydrate remained in the diffraction pattern with a water addition of 0.3 g/g. The SMCC formulation identified by NIR on the second day showed that nitrofurantoin monohydrate started to form after the first (0.1 g/g) addition of water (Figure 5C).

Solid-Water Interaction of Formulations Containing Amorphous Excipients

Hygroscopic modified starch was able to hinder the formation of nitrofurantoin monohydrate at higher water contents than SMCC but at lower water contents than L-HPC grade LH-21. On the first day, nitrofurantoin monohydrate began to transform after the addition of 1.5 g/g of water to the starch formulation, but the diffraction patterns included features of both anhydrous nitrofurantoin and nitrofurantoin monohydrate (Figure 4B). The determination by NIR showed that after a water addition of 1 g/g, the added water was seen only as free water and, thus, as a gradually increasing absorption maximum at around 1,900 nm (Figure 5B).

On the second day, nitrofurantoin monohydrate in the starch formulation was observed to form already after a water addition of 0.2 g/g (Figure 4C), but features of anhydrous nitrofurantoin remained. NIR on the second day revealed that nitrofurantoin monohydrate started to form after the second (0.2 g/g) addition of water (Figure 5C).

L-HPC (LH-21), which is also hygroscopic, hindered hydrate formation of nitrofurantoin at high water contents, even at a content of 4 g/g on the first day. It was difficult to determine whether features of monohydrous nitrofurantoin were present in the diffraction patterns or whether these features were only amorphous background from water. On the second day, features of nitrofurantoin monohydrate were present in the diffraction pattern with a water addition of 4 g/g. Determination by NIR showed that after a water addition of 3 g/g, the added water was seen only as free water, because the saturation point of NIR had been reached, and, thus, a gradually increasing absorption maximum was observed at around 1,900 nm (Figure 5D).

Drying in a VT-XRPD

To compare the behavior of 4 different wet formulations and determine the temperature above which monohydrous nitrofurantoin dehydrates, the heating process was performed in a VT-XRPD under ambient conditions. The relative amounts of nitrofurantoin monohydrate in the crystal structure of the wet masses heated at temperatures ranging from 25 to 250°C are shown in Figure 6. Wet masses were measured after overnight equilibration to ensure a uniform distribution of water. Dehydration behavior of nitrofurantoin monohydrate (form II) showed dehydration starting at 120 to 130°C, which is consistent with previous findings.[19] The relative amount of nitrofurantoin monohydrate in the 4 formulations varied depending on the properties of the

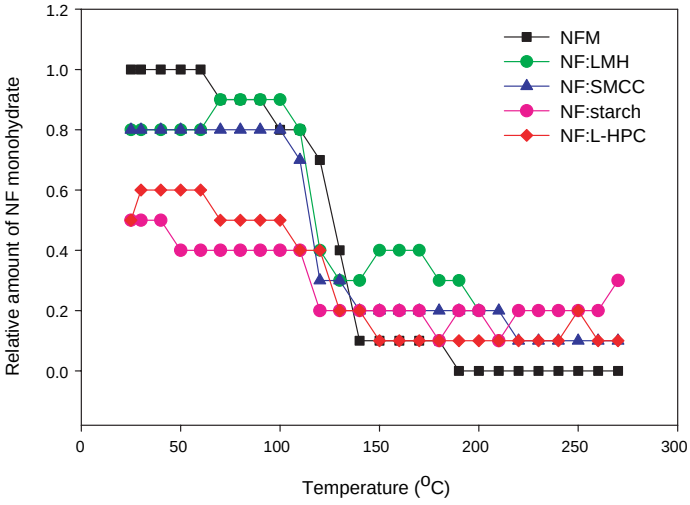

Figure 6. Relative amounts of nitrofurantoin monohydrate (NFM) in the crystal structure of nitrofurantoin wet masses after different water additions into the formulation on the second day. Formulations (1:1) with nitrofurantoin anhydrate (NF):LMH, NF:SMCC, NF:L-HPC, and NF:starch heated at temperatures ranging from 25 to 250°C using a VT-XRPD.

excipient used. The relative amount of nitrofurantoin monohydrate was highest in the formulations containing SMCC or LMH (0.8). The relative amount of nitrofurantoin monohydrate decreased rapidly from 0.8 to 0.3 or 0.4 when heated at about 120°C. In contrast, the relative amount of nitrofurantoin monohydrate in the formulations containing L-HPC or starch was only 0.5 at room temperature, decreasing gradually as a function of temperature. Some dehydration behavior of nitrofurantoin monohydrate was observed at 110 to 120°C with starch and at 120 to 130°C with L-HPC.

DISCUSSION

Role of Degree of Crystallinity in Solid-Water Interaction of the Formulation

Otsuka and Matsuda[20] studied the moisture sorption hydration kinetics of nitrofurantoin and found that the hydration rate of the mixture with LMH during storage at 95% RH at 40°C was 6.6 times higher than that of pure nitrofurantoin anhydrate. By contrast, the respective hydration rates of the mixture with microcrystalline cellulose (MCC) were about 7 times slower than those of nitrofurantoin anhydrate. The 2 mixtures showed no differences after storage at 0% to 82% RH and at 40°C. Our results were consistent with these; the hydration of nitrofurantoin containing LMH in the formulation was faster and was achieved with a lower water content than formulation containing SMCC. Similar findings have also been reported by Airaksinen et al.[25] Moreover, we did not observe any difference in nitrofurantoin formulations after storage at 0% to 75% RH for 2 weeks. In contrast with the sorption data by Otsuka and Matsuda,[20] we failed to distinguish any differences between the formulation containing SMCC and that containing LMH with nitrofurantoin anhydrate after storage at 85% or 95% for 2 weeks.

At low moisture content, moisture adsorption onto the surface is preferred in the case of such crystalline solids as LMH or nitrofurantoin anhydrate as a monolayer and with increasing moisture as multilayers.[16] At high-water activity (>0.85), the amount of water absorbed by crystalline powders is dependent on the packing density of the powders, which can be explained using the capillary condensation theory.[27] The deliquescence of LMH could also explain the sorption behavior of LMH-nitrofurantoin formulation.[20] In general, the moisture sorption isotherm of crystalline material may be affected not only by the chemical properties and structure of sorbent surface but also by the particle size distribution, specific surface area, deliquescence, and porosity of powders.

Relatively low percentages of amorphous material can absorb considerable amounts of water into their structure.[15] SMCC, like MCC, has a porous structure with both crystalline (approximately 70%) and amorphous regions (approximately 30%). Water molecules penetrate cellulose, particularly in the amorphous regions.[28] During water-cellulose interactions, water replaces the cross-linking hydrogen bonds between cellulose chains and loosens the structure of cellulose until capillary condensation occurs. The surface interaction of moisture directly with nitrofurantoin anhydrate at high RHs may be involved in the sorption behavior of the SMCC-nitrofurantoin formulation. Accordingly to Heidemann and Jarosz,[29] starch and L-HPC have a stronger affinity than SMCC for binding water. Therefore, at higher humidity levels, formulations containing starch or L-HPC were equilibrated to the equilibration moisture content more slowly than formulations containing SMCC, and drug stability increased in the formulations containing starch or L-HPC. Because the crystallinity of SMCC is much higher than that of L-HPC and starch, they could absorb more water than SMCC. The results showed that SMCC is able to delay hydrate formation of nitrofurantoin only at low-moisture contents, not at the amounts of water needed to form granules.

Modified starch (eg, Starch 1500) is partially pregelatinized maize starch that contains soluble (gelatinized) and insoluble fractions.[30] The insoluble fraction comprises intact starch grains. Pregelatinized starch has been chemically and/or mechanically processed to rupture all or part of the starch granules. Pregelatinized starch contains 5% free amylase, 15% free amylopectin, and 80% unmodified starch. Water vapor sorption by starch could be described by the same basic mechanism as MCC.[28] Water molecules have a strong affinity for starch because of the combination of an abundance of hydroxyl groups and a relatively open conformation of the glucose monomers that comprise starch.[31] Our results showed that modified, partially pregelatinized maize starch in the formulation is able to absorb more water than SMCC without hydrate formation of nitrofurantoin in the formulation. Although starch is able to take larger amounts of water into its internal structure, it was able to absorb less water than L-HPC in the formulation. It seemed that drug stability increased in the formulations containing starch, equilibrating to the equilibration moisture content more slowly than the SMCC formulation.

Amorphous L-HPC is used as an excipient in granulation and tableting because of its good binding and disintegrating properties. In L-HPC, only a small proportion (7% to 16%) of the 3 free hydroxyl groups per glucose subunit are converted by substituting hydroxypropoxyl groups; the hydroxypropyl group content of grade LH-21 is 10% to 13% (Shin-Etsu Chemical Co Ltd, Tokyo, Japan). Kawashima et al[32] reported that the hydrogen bonding between the unsubstituted hydroxy groups is more firmly formed than hydroxy groups of hydroxypropyl. L-HPC is insoluble in water but swells when it comes into contact with water.

SMCC (or MCC) absorbed less water than L-HPC, which is consistent with previous findings.[32] Because the hydroxy groups of MCC/SMCC are not substituted with hydroxypropyl groups, the intermolecular hydrogen bondings are strongly formed in the particle. Because L-HPC has a larger amorphous portion compared with MCC/SMCC, it can bind more water. The higher crystallinity of MCC/SMCC results in fewer free-hydroxyl groups in the MCC/SMCC particles that can form hydrogen bonding with the water molecule compared with L-HPC.

Role of Excipients in Drying Behavior of the Formulation

The drying phase is a critical step in many pharmaceutical processes. Drying is essentially a process of simultaneous heat and mass transfer. First, water molecules evaporate from the surfaces of particles, and water that remained within the particle must then diffuse toward the surface of the wet mass (granules) before it can be evaporated. The strength of the water-solid interaction depends on the level of hydrogen bonding possible within the lattice.[16] Crystal packing in the β-polymorph of an anhydrous form of nitrofurantoin has a layer structure.[18] The molecular packing in nitrofurantoin monohydrate I shows a layer structure, whereas monohydrate II (studied here) molecules have a herringbone arrangement.[17] The water molecules play an essential role in stabilizing these arrangements through hydrogen bonding of nitrofurantoin monohydrate. Each water molecule in monohydrate II links 2 nitrofurantoin molecules by hydrogen bonding. Monohydrate I has been shown to lose water at lower temperatures than monohydrate II.[19]

At the outset of drying in a VT-XRPD, the relative amount of nitrofurantoin monohydrate was highest in the formulations containing SMCC or LMH, because their structure uptakes a minimal amount of moisture, with nitrofurantoin anhydrate taking up the majority of water into the crystal lattice forming monohydrate. Formulations containing crystalline or partially crystalline excipients (LMH and SMCC) showed rapid dehydration behavior starting at 110 to 120°C, whereas dehydration of pure nitrofurantoin monohydrate started later (120 to 130°C). Monohydrate II showed dehydration at 127°C according to Caira et al.[19] The bigger particle size of crystallized nitrofurantoin monohydrate compared with excipient-nitrofurantoin monohydrate blends could affect the dehydration rate of water. Water molecules are contained in isolated cavities in nitrofurantoin monohydrate II, resulting in a higher temperature of dehydration.[19] At 120 to 170°C, the relative amount of nitrofurantoin monohydrate in the formulation with LMH is higher (0.4) than in the other formulations (approximately 0.2). The water of crystallization of LMH dehydrates at approximately 150°C. Some features of the diffraction patterns for anhydrous β-lactose can also be identified during the drying process at 150 to 170°C, in accord with previous reports.[33] This could explain the higher relative amount of nitrofurantoin monohydrate in the LMH formulation until the granules were completely dried at 170°C.

In contrast, the relative amount of nitrofurantoin monohydrate in the formulations containing L-HPC or starch was only 0.5, because they absorbed moisture into their amorphous structure gradually (ie, equilibrated slowly) and also delivered moisture slower than the crystalline forms using diffusion as a dehydration process. However, in the wet nitrofurantoin-hydroxypropylcellulose formulation, the relative amount of nitrofurantoin monohydrate decreased to 0.1 at 150°C.

The gelatinization of starch granules is governed by moisture content and temperature.[34] In an ample water environment, starch easily gelatinizes, typically in the temperature range of 60 to 100°C. The full gelatinization of starch, before the total transformation of nitrofurantoin anhydrate, could explain why the formulation with starch remained at the relative nitrofurantoin monohydrate amount of 0.2 until the end of drying. Diffusion mechanism would be interesting to study in future. Thus, it is important to know how different excipients in the formulation could change and affect the bioavailability of the final dosage form.

Implication to Preformulation

Sorbed moisture can markedly change the physical and chemical properties of polysaccharides by accelerating hydrolytic degradation, isomerization, and/or crystallization processes and by affecting the flow, compaction properties of the polymer, and the physical and chemical stability of solid-dosage forms.[35] The amount of water sorbed is dependent on the RH and the amount of water used in the manufacturing process, as well as on the polymer chemistry and the effects of the water on the structure of the solid.[36] This study demonstrates that it is important to understand the moisture sorption behavior of formulations to avoid phase transitions during drug processing and storage. With low-water contents, a spectroscopic approach enables phase transformations in the formulation to be identified.

When a particular crystal form is selected for formulation, ensuring that the crystal form in the final product remains unchanged is critical. Monitoring of the crystal form during the manufacturing process is especially important if dissolution or stability of the product is sensitive to solid-phase changes.[37] Those aspects of API, excipients, and manufacturing processes that are critical and that present a significant risk to product quality should be monitored, controlled, identified, and, finally, evaluated the effect of

their variation on the quality of the drug product.[4] In addition, solid-state transformation may cause variability in the tableting behavior of the final mass, as far as the different crystal forms may have different mechanical properties. During such steps as wet granulating, drying, and tableting, the possibility of a crystal form alteration must be considered. Real-time quality control leads in the optimal case to a reduction of end-product-release testing. Depending on the physical and chemical properties of API, the phase transformations could significantly change the bioavailability, processing characteristics, or stability of API. It is important to consider the critical formulation attributes, together with the available manufacturing process options, to address the selection of the manufacturing process and to confirm the expediency of the components, like excipients.[4] Optimizing the selection of excipients in the formulation could reduce processing-induced phase transitions during manufacturing and storage of final-dosage forms.

CONCLUSION

Excipients can significantly affect solid-state phase transitions in the formulation. It is important to recognize that quality cannot be tested into final products, but quality should be built in by design. Results of this study showed that the less crystalline excipient used in the formulation, the more water is absorbed into structure of the excipient. In this study, only amorphous excipient retarded hydrate formation of API at high water contents during wet granulation. Hygroscopic partially crystalline excipient in the formulation hindered hydrate formation of API at low-water contents. Crystalline excipient was unable to control hydrate formation of API. The correct selection of excipients in the formulation allows for control processing-induced phase transitions and improves the storage stability of the final dosage forms.

ACKNOWLEDGMENTS

We thank Pharmia Oy (Finland) for use of the Fourier Transform-NIR instrument. This study was financially supported by the National Technology Agency, TEKES (Finland), and by a grant from the Finnish Cultural Foundation (SA, Elli Turunen Foundation).

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