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Characterization of polymorphic solid-state changes using variable temperature X-ray powder diffraction

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Abstract

The aim of this study was to use variable temperature X-ray powder diffraction (VT-XRPD) to understand the solid-state changes in the pharmaceutical materials during heating. The model compounds studied were sulfathiazole, theophylline and nitrofurantoin. This study showed that the polymorph form of sulfathiazole SUTHAZ01 was very stable and SUTHAZ02 changed as a function of temperature to SUTHAZ01. Theophylline monohydrate changed via its metastable form to its anhydrous form during heating and nitrofurantoin monohydrate changed via amorphous form to its anhydrous form during heating. The crystallinity of SUTHAZ01, SUTHAZ02 and theophylline monohydrate were very high and stable. Nitrofurantoin monohydrate was also very crystalline at room temperature but during heating at lower temperatures the crystallinity decreased and started to increase strongly at the temperature where the sample had changed to the anhydrous form. The average crystallite size of sulfathiazole samples varied only a little during heating. The average crystallite size of both theophylline and nitrofurantoin monohydrate decreased during heating. However, the average crystallite size of nitrofurantoin monohydrate returned back to starting size at higher temperatures. These analyses showed that VT-XRPD can be used to effectively characterize polymorphic changes during heating.

Keywords: X-ray diffraction (XRD); Variable temperature X-ray powder diffraction (VT-XRPD); Polymorphism; Pseudopolymorphism; Crystal structure; Analysis; Sulfathiazole; Theophylline; Nitrofurantoin

1. Introduction

Many physical properties of pharmaceutical materials depend on the structure of the materials and thus it is necessary to know and understand the structure of the materials when preparing new formulations. The materials must go through many processes during preparing the pharmaceutical products and the structure of the materials can change during these different processes. Grinding is an often used pharmaceutical process to reduce particle size and to accelerate the solubility of materials. Grinding usually makes material more amorphous and it can also change the polymorph form of a material. The polymorph change of anhydrous caffeine from metastable form I to the stable form II by grinding has been reported [1].

Other processes like compression, granulation and drying have also similar effects on crystal structure as grinding. Compression also changes the polymorph form of anhydrous caffeine [1]. Granulation and drying are processes where temperature and air humidity have large effects on the material. The crystal structure and the physical properties may change a lot already when water leaves the crystals of the material. Sometimes drying is used to make a polymorph transition. Dehydration can start the formation of metastable anhydrous forms from carbamazepine dehydrate [2] and theophylline monohydrate [3,4].

The physical properties of metastable and stable forms can differ significantly. It has been reported that the property of metastable form of caffeine is totally different from that of the stable form of caffeine. The absorption of water for

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the metastable form is three times faster than that of stable form [5].

X-ray diffraction (XRD) is a very good method for structural studies of materials as it gives a lot of information about the structure of the materials and it is also non-destructive. XRD can be used to investigate the structures of many materials as simple a grain of salt, and as complex as a protein in the crystalline form [6]. An unknown material can be identified using the positions and the intensities of the Bragg reflections. The average crystallite size and strains in the crystals can be estimated from the shape of the reflections. XRD experiments also give information about the crystallinity and texture of the materials [7–10]. The polymorphic content of materials can be determined using XRD [11,12].

Variable temperature X-ray powder diffraction (VT-XRPD) is a method where XRD experiments can be done at different temperatures. VT-XRPD provides information about the solid-states of various reaction phases [13]. As usual the granulation and the drying are processes where different temperatures are used. In our previous publication we studied isothermic drying process and dried theophylline granules keeping the sample at the same heating temperature during 12 h [4]. Thus VT-XRPD can give direct information of the structure of materials used in the processes.

The aim of this study was to use variable temperature X-ray powder diffraction (VT-XRPD) in studying the polymorph changes in the pharmaceutical materials during heating. The model compounds studied were sulfathiazole, theophylline and nitrofurantoin.

2. Materials and methods

2.1. Materials

The experiments were made on recrystallized sulfathiazole, wet theophylline granules and recrystallized nitrofurantoin. The sulfathiazole samples were crystallized from *n*-propanol (analytical grade, Sigma–Aldrich Laborchemikalien, Seelze, Germany) and from water (Millipore). The theophylline monohydrate standard was prepared by dissolving anhydrous theophylline in distilled water at 60 °C and dried at room temperature until the moisture content was about 9%. The wet theophylline mass was performed using a planetary mixer (Kenwood KM400, Kenwood Ltd., UK). The batch size was 300 g of theophylline anhydrate (Ph.Eur., Orion Pharma, Espoo, Finland), and amount of purified water added to the dry material was 0.5 g/g. The mass was mixed for 5 min after the addition of water. The recrystallized nitrofurantoin monohydrate was prepared by dissolving anhydrous nitrofurantoin in distilled water at 90 °C.

2.2. VT-XRPD experiments

The samples were measured by using a variable temperature X-ray powder diffractometry (VT-XRPD) (Bruker axs D8, Germany). The VT-XRPD experiments were performed in symmetrical reflection mode with Cu Kα radiation (1.54 Å) using Göbel Mirror bent gradient multilayer optics. The scattered intensities were measured with a scintillation counter. The angular range was from 5° to 40° for sulfathiazole samples and from 5° to 50° or to 20° for theophylline samples and 5° to 35° for nitrofurantoin samples. The measurements were made with the steps of 0.05° and the measuring time was 1 s/step. The samples were measured at different temperatures from room temperature to a high temperature with the heating rate of 0.2 °C/s.

2.3. Data analysis

The estimation of the relative amount of crystal structure in the polymorph forms of the samples was based on the assumption that the experimental VT-XRPD intensity curve is a linear combination of the intensity of polymorph form components:

$$I_n = \sum_{i=1}^{N} \alpha_i I_i = \alpha_1 I_1 + \ldots + \alpha_N I_N$$

where I_n is the intensity of studied sample and α_i, α_1 and α_N are the fitted constant values to the polymorph components and I_i, I_1 and I_N are the intensities of the polymorph components. The amount of structure of polymorph components was estimated by fitting the diffraction curves of the components to the experimental diffraction curve of the samples [4,14–16]. The relative amount of polymorph form component was calculated as the ratio of the integrals of the intensities of the component and the studied sample.

The proportions of the SUTHAZ01 and SUTHAZ02 structures in the sulfathiazole samples during heating was estimated by fitting a linear combination of the diffraction curves of the recrystallized samples using *n*-propanol (SUTHAZ01) and water (SUTHAZ02) at room temperature to the experimental diffraction curve of sample.

The proportions of theophylline monohydrate and anhydrate in the granulated theophylline during heating were estimated by fitting a linear combination of the diffraction curves of the recrystallized monohydrate and anhydrate to the experimental diffraction curve of sample [17].

The proportions of nitrofurantoin monohydrate and anhydrate in the recrystallized nitrofurantoin was estimated by using the same method as in the case of theophylline. Recrystallized nitrofurantoin monohydrate and commercial anhydrate were used as components.

The average crystallite size (t) in the samples was calculated using the Scherrer formula from the width of the highest reflections:

$$t = \frac{0.9\lambda}{(B\cos\theta)}$$

where λ is the wavelength of the radiation, θ the half of the scattering angle and B was calculated using the formula:

$$B = (b_n^2 - b_1^2)^{1/2}$$

where b_n is the full width at half maximum (FWHM) of the diffraction peak of the sample and b_l the instrumental broadening, which is estimated as a FWHM of a reflection of a sample with large crystallites [7]. Here, a crystal Si sample was used.

The estimation of the crystallinity was based on the assumption that the experimental VT-XRPD intensity curve is a linear combination of intensity a crystalline and an amorphous component:

$$I_n = aI_c + bI_a$$

where I_n is the intensity of studied sample and a and b are the fitting constant values to the crystalline and amorphous components and I_c and I_a are the intensities of the crystalline and amorphous components.

The crystallinities of the samples were estimated by fitting the intensities of the crystalline and amorphous component to the experimental intensity curve [18,19]. The intensity curves from totally amorphous melted samples were used as the amorphous model intensity curves to the samples. The crystalline model intensity curves consisted only of the diffraction peaks. The crystallinities were calculated as the ratio of the integrals of the intensities of the crystalline component and the studied sample. The accuracy of these analysis are ±10%.

3. Results and discussion

3.1. Characterization of sulfathiazole samples

Fig. 1a and b present the measured VT-XRPD diffraction patterns for a recrystallized sulfathiazole sample from *n*-propanol and from water at the room temperature to 190 °C, respectively. The diffraction pattern of sulfathiazole samples at room temperature from *n*-propanol and water were near the polymorph forms I (SUTHAZ01) and III (SUTHAZ02), respectively [20].

The diffraction patterns of the sulfathiazole sample from *n*-propanol (SUTHAZ01) did not change much during heating from room temperature to 190 °C indicating its stable crystal structure. The main clear reflections were in the diffraction patterns and only the intensities of the reflections little change due to the preferred orientation of the crystals. The reflections of the diffraction pattern disappeared at the temperature of 200 °C and the sample changed to being totally amorphous indicating that the sample was melted.

The diffraction pattern of the sulfathiazole sample from water (SUTHAZ02) changed as a function of temperature. The intensities of the reflections changed. The reflections of polymorph form SUTHAZ02 decreased and the reflections of the polymorph form SUTHAZ01 increased.

The fitting indicated that the proportion of SUTHAZ02 structure decreased and the proportion of SUTHAZ01 structure increased as a function of temperature (Fig. 2). The pro-

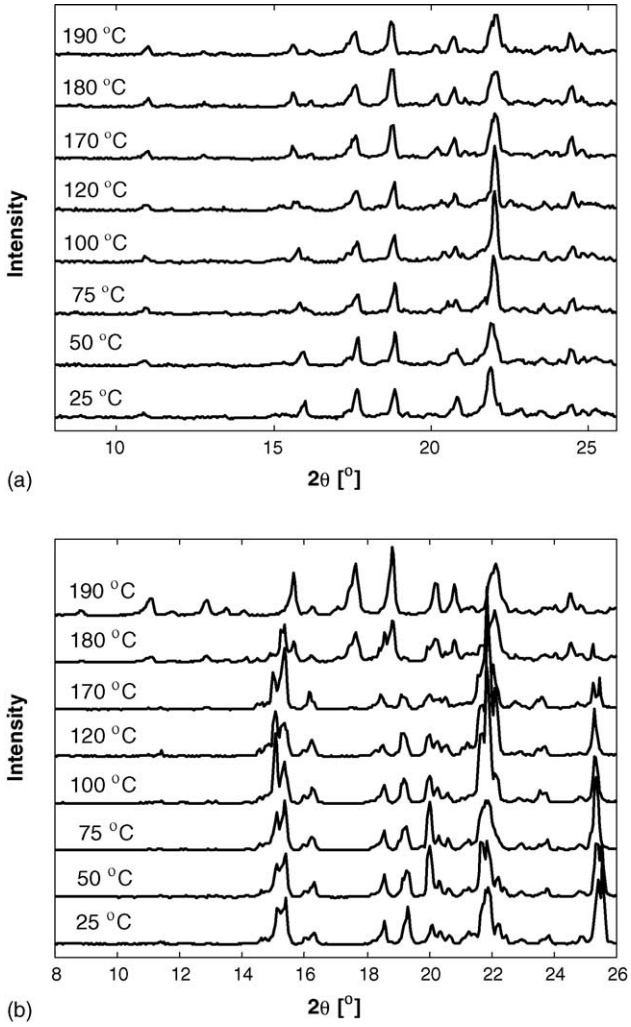


Fig. 1. (a) VT-XRPD diffraction patterns of the recrystallized STZ sample from *n*-propanol in the range of 25–190 °C; (b) VT-XRPD diffraction patterns of the recrystallized STZ sample from water in the range of 25–190 °C.

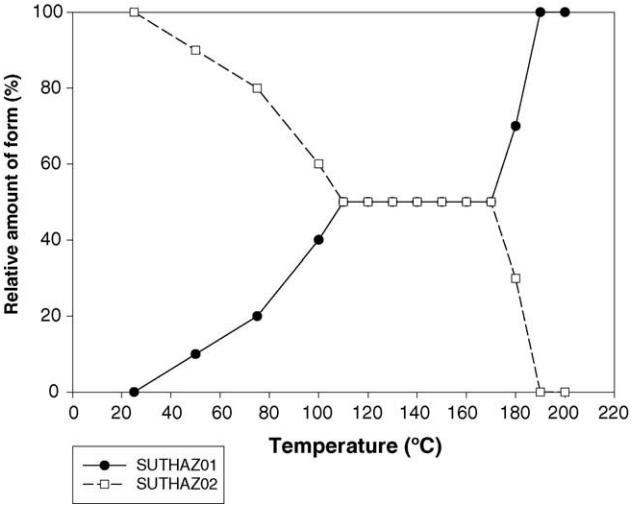


Fig. 2. Calculated relative proportions of SUTHAZ01 and SUTHAZ02 in the recrystallized STZ sample from water.

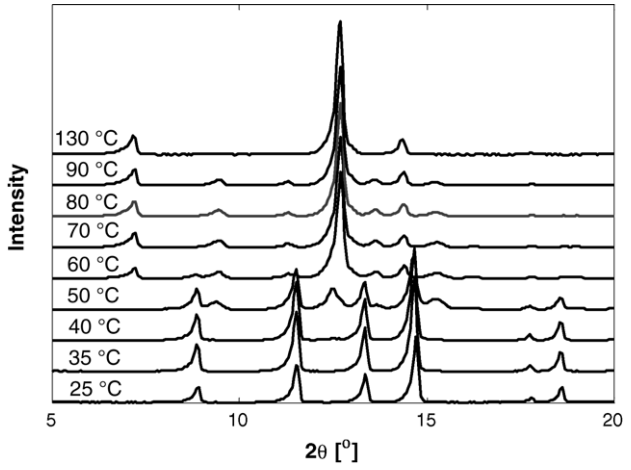


Fig. 3. VT-XRPD diffraction patterns of granulated theophylline at different temperatures.

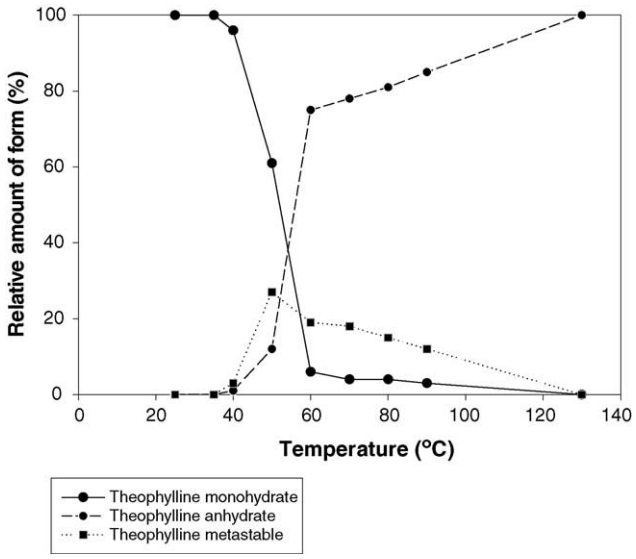


Fig. 4. Calculated relative amount of theophylline monohydrate, anhydrate and metastable in granulated theophylline.

portion of SUTHAZ01 structure increased significantly at 170 °C and the sample change totally to the SUTHAZ01 form at 190 °C.

The crystallinity of the sulfathiazole samples was very high about 98% and stable up to 200 °C before melting. The average crystallite size of sulfathiazole samples varied from 410 to 550 Å.

3.2. Characterization of theophylline samples

The diffraction pattern of our theophylline monohydrate resembles closely that of earlier presented monoclinic theophylline hydrate where $a = 13.30$ Å, $b = 15.42$ Å, $c = 4.47$ Å and $\beta = 98.81$ determined by Wang et al. 1974 should reverse [21] and the diffraction pattern of anhydrous theophylline agreed with the earlier presented orthorhombic anhydrous theophylline where $a = 8.50$ Å, $b = 24.64$ Å and $c = 3.83$ Å [22]. Our anhydrous theophylline also resembles earlier presented theophylline anhydrate type II [23,24].

Fig. 3 presents the measured VT-XRPD diffraction patterns of theophylline granules at different temperatures. The diffraction pattern of the granules at room temperature agreed with that of theophylline monohydrate. The diffraction pattern of the sample was very similar up to 40 °C but changed very clearly at 50 °C. The reflections of monohydrate have decreased and the diffraction pattern also included new reflections. These new reflections are from theophylline anhydrate and the metastable form of theophylline [3,4]. The crystal structure had changed. The fitting indicated that the amount of the crystal structure of anhydrous form increased little (to 12%), the metastable form increased a lot (to 27%) and monohydrous form decreased (to 61%) (Fig. 4). After the 50 °C the reflections of monohydrate decreased and the reflections of anhydrate increased as a function of temperature. The relative amounts of the monohydrous and metastable form decreased and the amount of anhydrous increased. The diffraction pattern of the sample changed to the anhydrous form at 130 °C.

The granulated theophylline was very crystalline and the crystallinity varied only from 92 to 95%. The average crystallite size of the theophylline was 840 Å at room temperature and up to 40 °C and it decreased to 540 Å at 50 °C where the proportion of crystal structure of the metastable anhydrous form increase significantly.

The reflection of monohydrate shifted to smaller scattering angles as a function of temperature up to 60 °C indicating that the heating had increased the distance of the lattice planes. The average crystallite size of monohydrous theophylline decreased strongly when the reflections shifted to smaller scattering angles. In the same time the structure of theophylline monohydrate decreased and anhydrous theophylline increased. This means that the amount of water in the theophylline monohydrate crystals had decreased. The amount of water in the crystals decreased as a function of temperature which explains the decrease of the crystallite size.

The measured diffraction patterns of anhydrous form theophylline was very similar at different temperatures indicating a stable crystal structure and the properties of the polymorph form thus differed from that of the monohydrous form.

3.3. Characterization of nitrofurantoin samples

The diffraction pattern of our recrystallized nitrofurantoin closely resemble that of earlier presented nitrofurantoin monohydrate and our nitrofurantoin anhydrate agreed with the earlier presented nitrofurantoin anhydrate determined by Otsuka et al. [25].

Fig. 5 presents the measured VT-XRPD diffraction patterns of recrystallized nitrofurantoin at different temperatures. The diffraction pattern of the sample changes as a function of temperature.

The fitting indicated that the proportion of nitrofurantoin monohydrate crystal structure decreases and the anhydrous

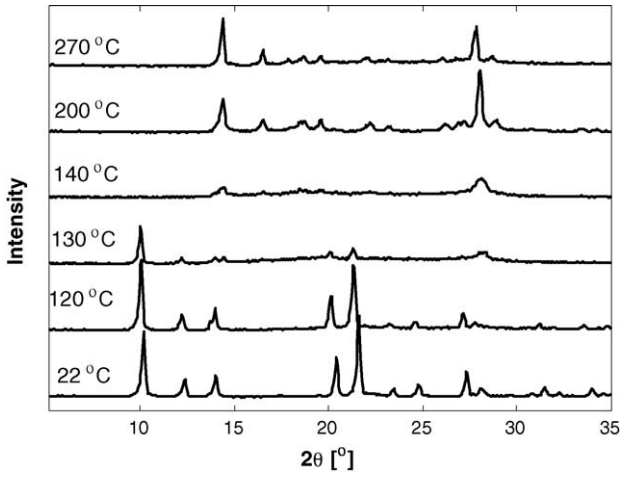


Fig. 5. Measured VT-XRPD diffraction patterns of recrystallized nitrofurantoin at different temperatures.

form increases as a function of temperature (Fig. 6). At 130 °C the proportion of the anhydrous form has increased to 64% and at 200 °C the sample has changed totally to the anhydrous form.

The recrystallized nitrofurantoin (nitrofurantoin monohydrate) was very crystalline (about 90%) but the crystallinity started to decrease at 120 °C and decreased very strongly at 130 °C (to 55%) (Fig. 7a). The crystallinity started to increase strongly at 200 °C where the sample had changed to the anhydrous form.

The average crystallite size of the nitrofurantoin monohydrate decreased strongly at 140 °C where the crystallinity was the smallest and increased at 200 °C where the crystallinity increased and the sample was in the anhydrous form (Fig. 7b).

Fig. 8 presents the measured VT-XRPD diffraction patterns for anhydrous form nitrofurantoin at different temperatures. The form of the diffraction patterns was very similar up

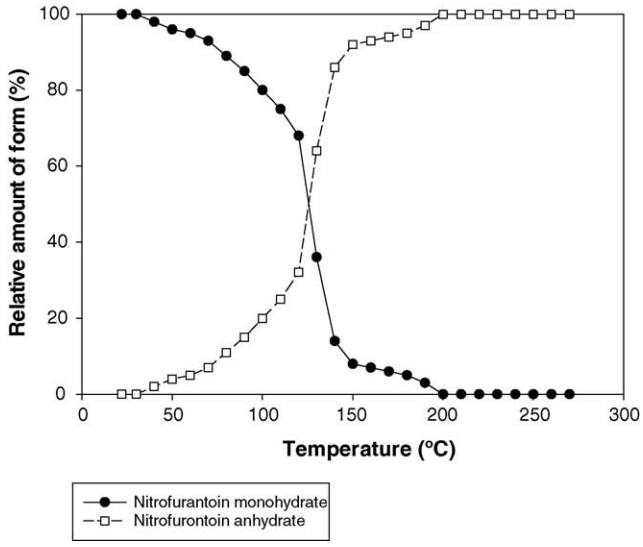
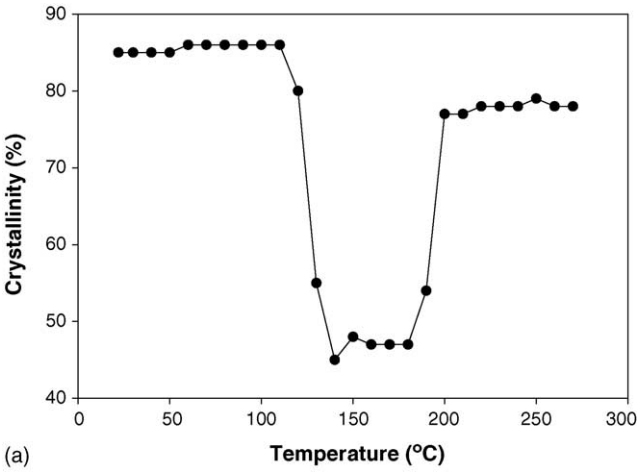


Fig. 6. Calculated relative amount of nitrofurantoin monohydrate and anhydrate in recrystallized nitrofurantoin.



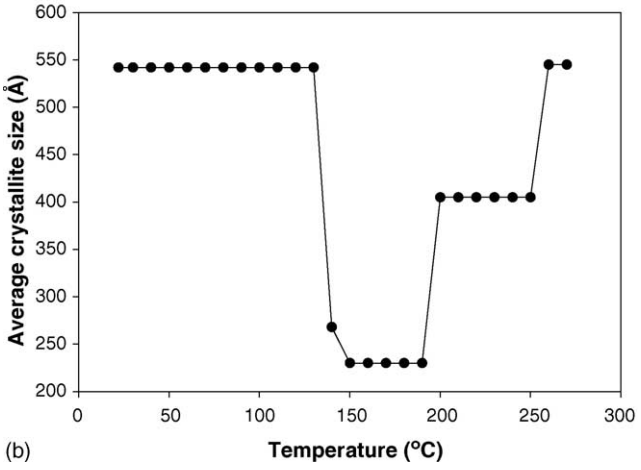


Fig. 7. (a) Calculated crystallinity of recrystallized nitrofurantoin at different temperatures; (b) average crystallite size of recrystallized nitrofurantoin at different temperatures.

to 200 °C indicating the same crystal structure. However, the reflections at about 14.5° and at 28.8° (2θ) shifted to smaller scattering angles as a function of temperature indicating that the heating had increased the distances between the lattice planes. The diffraction pattern of the sample changed very clearly at the temperature of 270 °C where the sample had partly melted.

The anhydrous form nitrofurantoin was also very crystalline about 90% and stable up to 260 °C and decreased to 6% at 270 °C. The average crystallite size of anhydrous form nitrofurantoin varied from 410 to 550 Å.

Preferred orientation of the crystals is very usual in many pharmaceutical materials and it makes difficult to the estimations of amount of polymorph forms. The form of the reflections of many materials are not usually even and symmetric, which makes difficulties to the calculations of crystallite sizes. However, the changes in the polymorph forms and crystallite sizes can be identified in sulfathiazole, theophylline and nitrofurantoin during heating by using VT-XRPD. The polymorphic forms of the samples behave differently during heating. Thus it is very important to know the polymorph

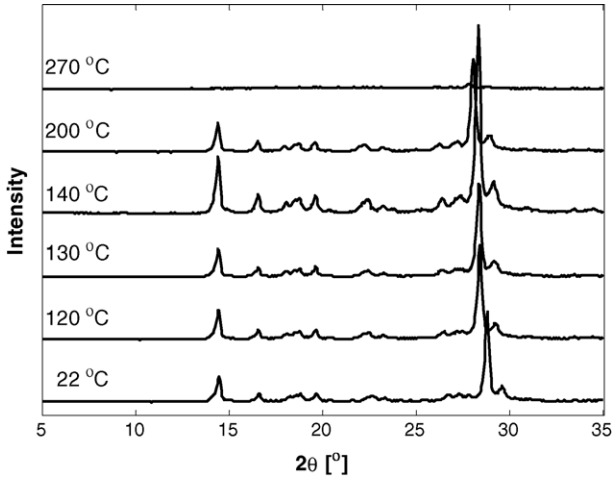


Fig. 8. VT-XRPD diffraction patterns of the anhydrous form of nitrofurantoin at different temperatures.

forms and possible changes in the polymorph forms for the formulations of pharmaceutical materials.

4. Conclusions

The polymorphic changes can be determined and quantitated using VT-XRPD diffraction. VT-XRPD diffraction gives information about proportions of crystal structure of polymorph forms, crystallinity and average crystallite size of samples at different temperatures. VT-XRPD can be used to effective characterize polymorphic changes during heating. The analysis showed that the polymorph form of SUTHAZ01 was very stable and SUTHAZ02 changed as a function of temperature to SUTHAZ01 in the case of sulfathiazole. Theophylline monohydrate changed via the metastable form to the anydrous form during heating and nitrofurantoin monohydrate changed via amorphous form to the anhydrous form during heating.

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