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Comparison of the effects of two drying methods on polymorphism of theophylline

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Abstract

Processing-induced transformations in drug formulation may induce adverse biopharmaceutical changes in the finished product. During the drying phase of wet granulation, theophylline monohydrate transforms either the stable (form I), or a polymorphic, metastable (form I*) form of anhydrous theophylline. We investigated the effect of two drying methods (multichamber microscale fluid bed dryer MMFD) or variable temperature X-ray powder diffractometer (VT-XRPD) on the relative amounts of the different theophylline forms remaining in the dried granules. Granules were analyzed using XRPD and near-infrared spectroscopy. Form I* was the predominant form of theophylline after drying at 40–50 °C with both drying techniques. Although drying at temperatures over 50 °C produced mostly form I, more than 20% of form I* remained even at 90 °C when drying in MMFD. In these conditions, humidity had little influence on the amount of form I* in the granules. In contrast, drying in a VT-XRPD at 60 °C produced form I already during the first 15 min. Using additional drying methods, including MMFD, during the preformulation stage can be more informative about the possible polymorphic transformations and their underlying mechanisms, such as triboelectrification or recrystallization, in drug ingredients during the manufacturing process.

Keywords: X-ray powder diffraction; Fluid bed; Drying; Polymorphism; Metastable anhydrous theophylline

1. Introduction

Wet granulation is a widely used manufacturing process in the pharmaceutical industry. It is usually done in the form of fluid bed granulation using a binder liquid consisting mostly of water and some polymer. When water evaporates, the binder solidifies between the particles, forming a strong solid bond. The drying phase in wet granulation consists in removing part of the liquid from a solid by thermal methods to obtain the moisture level best suited to the following process. Drying is essentially a process of simultaneous heat and mass transfer. Heat, necessary for evaporation, is transferred from the surroundings to the particle surfaces by convection and from there further into the particle by conduction. Water is transported in the opposite direction as a vapor; on the surface it evaporates and passes on by convection to the surroundings. During a fluid bed drying process water loss typically occurs in two stages: heat-transfer limited and mass transfer limited phases. During the heat-transfer limited phase the air temperature surrounding the material

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is reduced as water evaporates from the wet surface of particles in the bed, and the rate of drying and the bed temperature remain constant. During the mass transfer limited phase, drying occurs when water evaporates from the surface and the remaining water diffuses to the surface of the granules.

The drying cycle for all solids can be divided into three distinct phases: a heating phase, a constant rate of evaporation phase, and a falling rate of evaporation phase (Cooper et al., 1961; Terrier de la Chaise and LePerdriel, 1972). The drying rate is constant since the surface is saturated with water, and during air drying water is drawn to the surface by capillary forces. Dehydration reactions are influenced by a number of factors, including crystal packing, humidity and temperature, but hydrogen bonding and tunnel areas inside crystals are the two most important factors (Byrn et al., 1999; Sun et al., 2002). If the granules are tightly packed, air cannot take the place of water, and capillary forces play only a minor role. Under such conditions water is no longer drawn to the surface and as water continues to evaporate, the water content of the capillaries decreases. When the surface water content falls below a critical value, the drying rate decreases gradually until the surface is dry. Finally, the moisture content of granules reaches a thermodynamic equilibrium with the surrounding air (Hlinak and Saleki-Gerhardt, 2000).

During wet granulation of theophylline starting material, theophylline anhydrate incorporates water into the lattice and is transformed to theophylline monohydrate. When the wet theophylline granules are dried, the theophylline monohydrate either reverts back to the anhydrous form or is transformed to metastable anhydrous theophylline, a polymorph of theophylline anhydrate (Phadnis and Suryanarayanan, 1997). Whenever a wet suspension containing a drug substance is dried, the possibility exists that a change in its crystal state will take place. Granules and crystalline solids, like theophylline, should be relatively easy to dry due to the extensive distribution of water within the capillaries and the large water tunnels (Terrier de la Chaise and LePerdriel, 1972). The shape, size and number of the water tunnels, and the number and strength of hydrogen bonds between the solvent and the host compound may also play a role in preventing solvent molecules from escaping the crystals (Byrn et al., 1999). Packed crystals of theophylline monohydrate have relatively large tunnels filled with water molecules, and crystals of theophylline hydrate do not effloresce. The drying process may not completely remove all the moisture. After wet granulation, granules are usually not dried to zero moisture; it is practical to maintain a residual amount of moisture in the granulation, e.g. to avoid excess granule attrition during drying phase and to allow successful tabletting process. The level of residual humidity of the granulation process is one of the main factors in ensuring adequate compression (Terrier de la Chaise and LePerdriel, 1972). The combination of solvent and drying conditions provides a suitable environment for the generation of new polymorphs (Brittain and Fiese, 1999).

Theophylline is known to exist either as the anhydrate or monohydrate. Anhydrous theophylline has two stable polymorphic forms, one of which is stable at high temperatures and the other at room temperature (Suzuki et al., 1989). In addition, Phadnis and Suryanarayanan (1997) have described an anhydrous metastable form of theophylline that has a different X-ray diffraction (XRD) pattern than that of the stable anhydrous stable phase. Two modifications of anhydrous theophylline form have been identified also by differential scanning calorimetry (DSC) and infrared (IR) spectrometry (Suzuki et al., 1989). The metastable anhydrous theophylline (form I*) is an intermediate metastable polymorph of anhydrous theophylline that is produced by the dehydration of the monohydrate, but the metastable form was not found as an intermediate during hydration of stable anhydrous theophylline phase. Phadnis and Suryanarayanan (1997) suggested that the metastable form is a desolvated solvate and is unstable under ambient conditions. Temperature, water vapor pressure and the excipients in the formulation are able to affect the kinetics of the transition from metastable to stable anhydrous theophylline (Phadnis and Suryanarayanan, 1997). Because a metastable phase has a higher free energy than its stable counterpart, it has increased reactivity. During storage, the metastable form is expected to transform to the stable form. Any phase change due to polymorphic interconversions, desolvation of solvates, formation of hydrates or changes in the degree of crystallinity can alter the bioavailability of the drugs (Vippagunta et al., 2001).

The aim of this study was to investigate the effects of different drying conditions on the relative amounts

of different polymorphs of theophylline remaining in the dried granules during the preformulation stage. Two drying techniques (fluid bed and simulated tray drying) and two different drying conditions (involving various temperatures and two humidity levels) in a fluid bed dryer were investigated. Wet theophylline granules were dried using a multichamber microscale fluid bed dryer (MMFD), and a variable temperature X-ray powder diffractometer (VT-XRPD). X-ray powder diffraction (XRPD) was used to analyze the polymorphism of the theophylline granules, and the near-infrared (NIR) spectroscopic method (in-line and off-line) was used to monitor the dehydration of theophylline granules.

2. Materials and methods

2.1. Preparation of granules

Wet massing was performed using a planetary mixer (Kenwood KM400, Kenwood Ltd., UK). The batch size was 300 g of theophylline anhydrate (Ph.Eur., grade 200 M, Orion Pharma, Espoo, Finland), and 0.5 g g^{-1} purified water added to the dry material. The masses were mixed for 5 min after the addition of water. The wet granules were sieved, and fractions ranging from 1 to 2 mm was used in further analysis.

Fluid bed drying of theophylline granules was performed using a multichamber microscale fluid bed dryer (MMFD, Ariacon Oy, Turku, Finland) module with a process air control unit (Ilmasäätö Oy, Turku, Finland). The batch size was 10 ml and the airflow rate was 600 ml s^{-1}. The temperature of the inlet air was varied from 30 to 90 °C with steps of 10 °C. Moisture content of process air was less than 0.5 g water per m^3 of inlet air (i.e. dry inlet air) or 7.6 ± 0.3 g water per m^3 of inlet air (i.e. ambient inlet air). Dried granules were divided in half and then one sample was measured by NIR and another one by XRPD. Process monitoring and control were automated, and critical process parameters were logged (Räsänen et al., 2003, 2004).

2.2. Moisture content of granules

Moisture content of granules was determined using an infrared (IR) dryer (Sartorius Thermocontrol YTC01L, Sartorius Göttingen, Germany). The samples (2 g) were heated at 130 °C in the IR dryer until the rate of weight loss dropped to 0.1% in 50 s.

2.3. X-ray powder diffractometry

X-ray diffraction patterns were measured using an X-ray powder diffraction (XRPD) theta–theta diffractometer (Bruker axs D8, Bruker AXC GmbH, Karlsruhe, Germany). The XRPD experiments were performed in symmetrical reflection mode with CuK_α radiation (1.54 Å) using Göbel Mirror bent gradient multilayer optics. The scattered intensities were measured with a scintillation counter. The angular range was 5–20° with the steps of 0.05°, and the measuring time was 1 s per step (3° 2θ min^{-1}). The fluid bed dried granules were measured at room temperature.

The tray drying process was simulated in the XRPD. The wet granules were placed into the variable temperature holder of an X-ray powder diffractometer (VT-XRPD). The wet granules and theophylline monohydrate were heated to 40, 50, 60 or 70 °C, and maintained at the target temperature for 15 h. X-ray diffraction patterns were obtained during the drying process. The diffraction patterns of the granules were measured every 15 min during the first 3 h and thereafter every hour for 12 h. This method made it possible to follow phase transformations from theophylline monohydrate to anhydrate.

2.3.1. XRPD data analysis

The structure of anhydrous theophylline, of theophylline monohydrate and of the metastable form of theophylline in theophylline granules was estimated by fitting a linear combination of the diffraction curves of anhydrous theophylline and theophylline monohydrate to the experimental diffraction curve of each sample. The amount of the two theophylline components in each sample was calculated as the ratio of the integrals of the intensities of the standards (theophylline anhydrate and monohydrate) and the studied sample. The remainder was assumed to be the metastable form. The accuracy of the XRPD quantification method is approximately ±10%. The accuracy of our XRPD method and repeatability of MMFD were tested on drying granules at 30, 50, 70 and 90 °C using MMFD (dry inlet air), when $n = 4$ at each temperature (Fig. 2A). No replicate measurements were performed from other samples.

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

$$t = \frac{0.9\lambda}{(2B\cos\theta)} \quad (1)$$

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

$$B = (b_n^2 - b_l^2)^{1/2} \quad (2)$$

where b_n is the full width at half maximum (FWHM) of the diffraction peak of the sample; and b_l is the instrumental broadening which is estimated as a FWHM of a reflection of a sample with large crystallites (Cullity, 1978). Here a crystal Si sample was used.

2.4. Near-infrared spectroscopy

Off-line near-infrared (NIR) spectra were measured with a Fourier Transform near-infrared (FT-NIR) spectrometer (Bomem MD-160 DX, Hartmann & Braun, Quebec, Canada) using Bomem-GRAMS software (v. 4.04, Galactic Industries Inc., Salem, NH, USA) and Teflon as reference (99% reflective Spectralon, Labsphere Inc., North Sutton, NH, USA) (Räsänen et al., 2001). The spectra were measured through the bottom of a glass vial containing the sample. The measurements were carried out in triplicate. The spectra were recorded over a range of 10 000–4000 cm^{-1} with a resolution of 16 cm^{-1} and they were averaged over 32 scans. Second derivative transformations of absorbance, $\log(1/R)$, were performed with 11-point Savitzky–Golay smoothing (Savitzky and Golay, 1964) using Matlab software (v. 5.3, MathWorks Inc., Natick, MA, USA).

In-line moisture measurement was performed using multi-channel NIR spectroscopy with a fibre optic probe (Prototype, VTT Electronics, Finland) (Rantanen et al., 1998; Räsänen et al., 2003). Using three wavelengths, apparent absorbance of water (AWA) was calculated as follows:

$$\mathrm{AWA} = \frac{-\log(I_x/I_{x,\mathrm{ref}}) + \log(I_y/I_{y,\mathrm{ref}})}{-\log(I_z/I_{z,\mathrm{ref}}) + \log(I_y/I_{y,\mathrm{ref}})} \quad (3)$$

where I is intensity (x referring to 1998 nm signal, y to 1813 nm signal and z to 2214 nm signal) and ref is intensity using aluminum column reference at the corresponding wavelength channel. The reflectance at 1998 nm was used as a water indicator. The reflectance at 1813 nm was used for baseline correction and the reflectance at 2214 nm for normalization.

3. Results and discussion

3.1. Characterization of polymorphic forms

The granules were measured with X-ray powder diffractometry and near-infrared (NIR) spectrometry to determine the relative amounts of different polymorphic forms of theophylline. The diffraction pattern of the theophylline monohydrate (form II according to Phadnis and Suryanarayanan, 1997) agreed with that previously presented for monoclinic theophylline hydrate, where $a = 4.5$ Å, $b = 15.4$ Å, $c = 13.1$ Å and $\beta = 97.8^\circ$ (Sun et al., 2002) and characteristic peaks of theophylline monohydrate were 8.8, 11.5, 13.3 and 14.7° 2θ (powder diffraction file 26-1893, ICDD, USA). The diffraction pattern of the stable anhydrous theophylline (form I) used here closely resembled the intensity curve previously presented for orthorhombic theophylline anhydrate, where $a = 8.50$ Å, $b = 24.64$ Å and $c = 3.83$ Å (powder diffraction file 27-1977, ICDD, USA) and characteristic peaks of theophylline anhydrate were 7.2, 12.6, 14.5° 2θ. The diffraction pattern of the metastable anhydrous theophylline (form I*) agreed with results previously presented by Phadnis and Suryanarayanan (1997) despite the fact that the sample also contained some monohydrous and stable anhydrous theophylline. The characteristic peaks of metastable anhydrous theophylline were 9.4, 11.3, 12.5, 13.5 and 15.4° 2θ.

3.2. Polymorphic transition of theophylline in the dried granules

3.2.1. Theophylline polymorphism after drying in fluid bed

Fig. 1 shows the measured XRPD diffraction patterns of theophylline granules dried using an MMFD at different temperatures and two different moisture contents of inlet air. The diffraction pattern of the sample included both forms I (anhydrate) and I* (metastable) when dried at 30 °C using dry inlet air (Fig. 1a). The

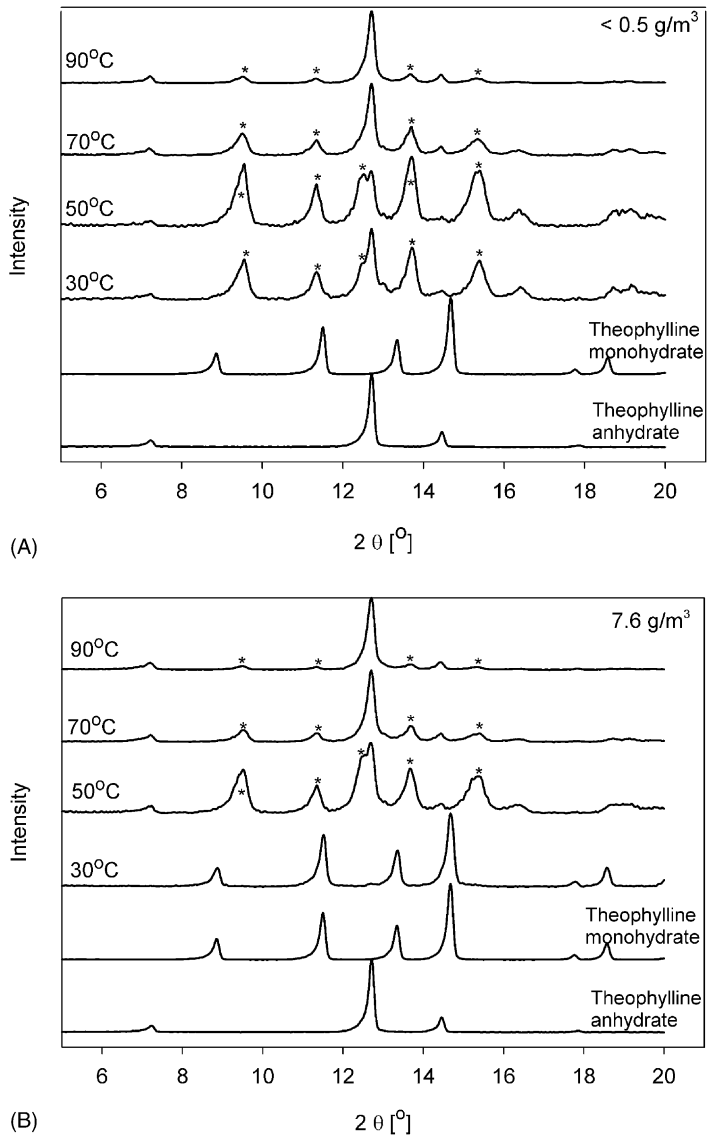

Fig. 1. (a) X-ray powder diffraction (XRPD) patterns of theophylline granules dried using a multichamber microscale fluid bed dryer (MMFD) at temperatures ranging from 30 to 90 °C using dry inlet air (under 0.5 g m^{-3}). (b) XRPD patterns of theophylline granules dried using MMFD at temperatures ranging from 30 to 90 °C using ambient inlet air (7.6 g m^{-3}). Note the characteristic peaks of theophylline anhydrate metastable form (∗). XRPD patterns of theophylline monohydrate and theophylline anhydrate at room temperature are shown below as controls.

relative amounts of forms I, I* and II (monohydrate) in the crystal structure were 30, 65 and 10%, respectively (Fig. 2a). The relative amount of form I* was highest (75%) in the granules dried at 50 °C using dry inlet air. Increasing the drying temperature to 90 °C did not change the diffraction patterns, but the intensities of reflections characteristic of form I* decreased, while the relative amount of form I* in the crystal structure was still 35% after drying at 90 °C. However, when the sample was dried at 30 °C, but using

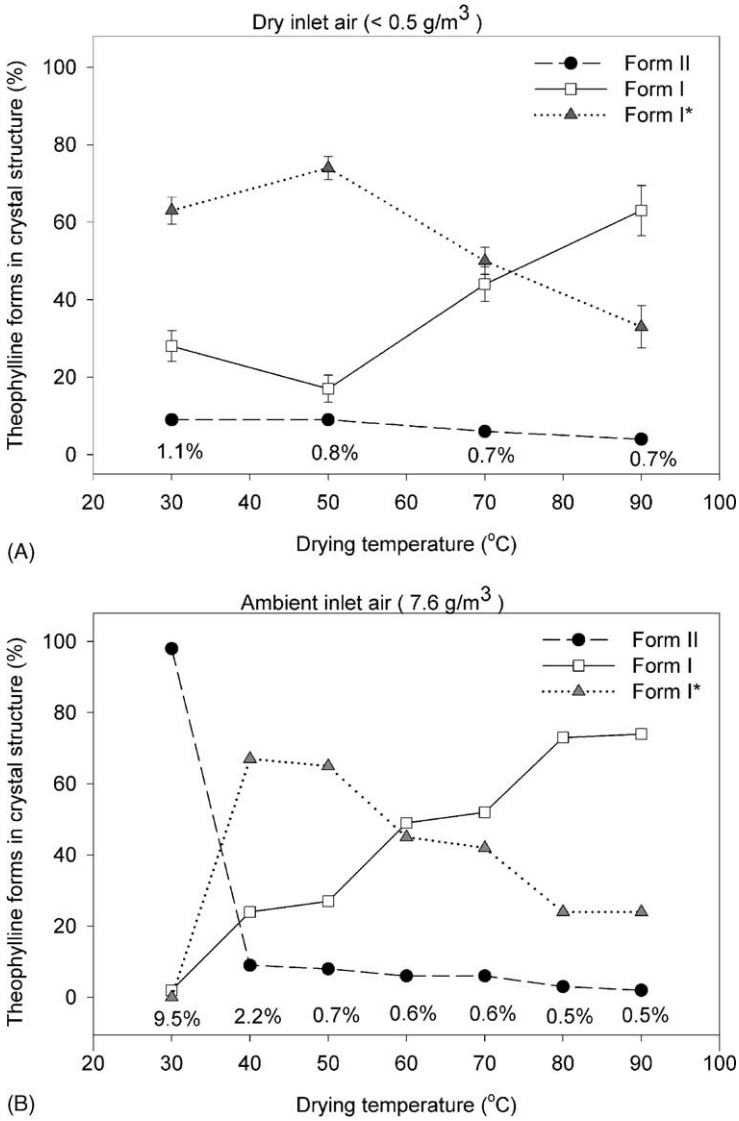

Fig. 2. The relative amounts of theophylline anhydrate forms I, I* and monohydrate II in the crystal structure of theophylline granules dried at 30, 50, 70 and 90 °C using a multichamber microscale fluid bed dryer (MMFD). The moisture content of inlet air was under 0.5 g m^{-3} (dry inlet air), $n = 4$ (a) and the moisture content of inlet air was 7.6 g m^{-3} (ambient inlet air), $n = 1$ (b). Percentage values represent the moisture contents of dried granules.

ambient inlet air (relative humidity, RH is ∼30%), the diffraction pattern closely resembled the pattern characteristic of form II (Fig. 1b), and the relative amount of form II in the crystal structure was still about 100% (Fig. 2b). The amount of form II decreased very clearly at temperatures over 30 °C. Almost all of the reflections of form II disappeared and new reflections representing forms I and I* emerged after drying at 40 °C (∼15% RH). At 40 °C, the relative amount of form I* was increased up to 70%, which is the highest relative amount of form I* with ambient inlet air (Fig. 2b, 40 °C). At 50 °C (∼9% RH) the relative amount of form I* was still high (65%) in the crystal structure, but decreased to 45% at 60 °C (∼6% RH), and the rel-

ative amount of form I increased from 25% (at 50 °C) to 50% at 60 °C (Fig. 2b). At 70 °C (∼3% RH), the relative reflections of form I* decreased to 40% and these of form I increased to 50% (Figs. 1b and 2b). Drying at the highest temperatures (80–90 °C) further decreased the relative amount of form I*. However, after drying at 90 °C (less than 2% RH), the granules still had 25% of form I* remaining in their structure (Fig. 2b). Moisture content of granules dried at or above 50 °C was 0.5–0.8% at both inlet air humidities (Fig. 2a and b).

As expected, the relative amount of water in the crystals decreased as a function of temperature, which probably explains the decrease of the crystallite size with increasing temperatures. According to Byrn et al. (1999), the breaking of hydrogen bonds in the water molecules is the first step in the dehydration reaction. The second step is the collapse of the hydrate crystal structure into that of anhydrate. For granules dried in the MMFD the average crystallite sizes of dried granules varied from 320 to 450 Å at different drying temperatures with dry or ambient inlet air, whereas the average crystallite size of theophylline monohydrate in the wet mass at room temperature was 840 Å. In general, the granules dried by ambient inlet air had a smaller crystallite size than granules dried by dry inlet air. However, crystallite size changed irregularly at drying temperatures ranging between 40 and 60 °C, while the moisture content in the crystals remained relatively constant, but the crystallite size became symmetrical again at 70 °C. The strain presumably disappeared at 70 °C, as the reflection became symmetrical. This is consistent with finding of Hüttenrauch and Keiner (1979) that the number of lattice defects in α-lactose monohydrate increased linearly with the loss of water. Solid-state reactions, especially dehydration reactions, begin with crystal defects (Byrn et al., 1999). The dehydration temperature and the reaction time depend on the extent of these defects. The extent and rate of removal of hydrate water from, e.g. milled lactose monohydrate depends on both the drying temperature and the intensity of the mechanical pretreatment of the material (Hüttenrauch and Fricke, 1981). This effect seems to be due to the degree of disorder of the crystals and to their mechanical activation, so that lattice defects promote the hydrate removal.

3.2.2. Theophylline polymorphism after drying in a VT-XRPD

In order to compare the two different drying methods and to determine the temperature above which metastable anhydrous theophylline does not form, the drying process was simulated in a VT-XRPD with ambient conditions. The relative amounts of theophylline forms in the crystal structure in the granules dried at 40–70 °C are shown in Fig. 3. The relative amount of form II (monohydrate) in the crystal structure decreased from 100 to 10% in 90 min when dried at 40 °C (Fig. 3a) and then it decreased gradually to 5% in approximately 15 h. The relative amount of form I* (metastable) started to form at the beginning of the drying process (after 15 min 20% of crystal structure), and the maximum relative amount of form I* in the crystal structure was 40% after 75 min. Form I (stable) also started to form at beginning of the drying process, and the relative amount of form I increased gradually until 70% and remained there. Accordingly, after about 15-h drying time at 40 °C, the relative amounts of forms I, I* and II remaining in the crystal structure were 75, 20 and 5%, respectively (Fig. 3a).

The relative amount of form II in the crystal structure decreased rapidly during the first 15 min of drying at 50 °C from 100 to 10% (Fig. 3b). After 15 min the relative amount of form I* in the crystal structure was already 40%. Form I also started to form immediately at the beginning of the drying process as expected, and the relative amount of form I in the crystal structure was 50% after 15 min drying time. After about 15 h drying time at 50 °C, the relative amounts of forms I, I* and II remaining in the crystal structure were 75, 20 and 5%, respectively. The relative amount of form II in the crystal structure decreased during the first 15 min from 100 to 10% when dried at 60 °C (Fig. 3c). The relative amount of form I* in the crystal structure was only 5% after 15 min and 0% after 30 min. Form I started to form immediately at the beginning of the drying process, and the relative amount of form I in the crystal structure was already 90% after 15-min drying time. After 5-h drying time at 60 °C, the relative amount of form I in the crystal structure was 100%. The results obtained when drying the granules at 70 °C were identical to those obtained at 60 °C. For

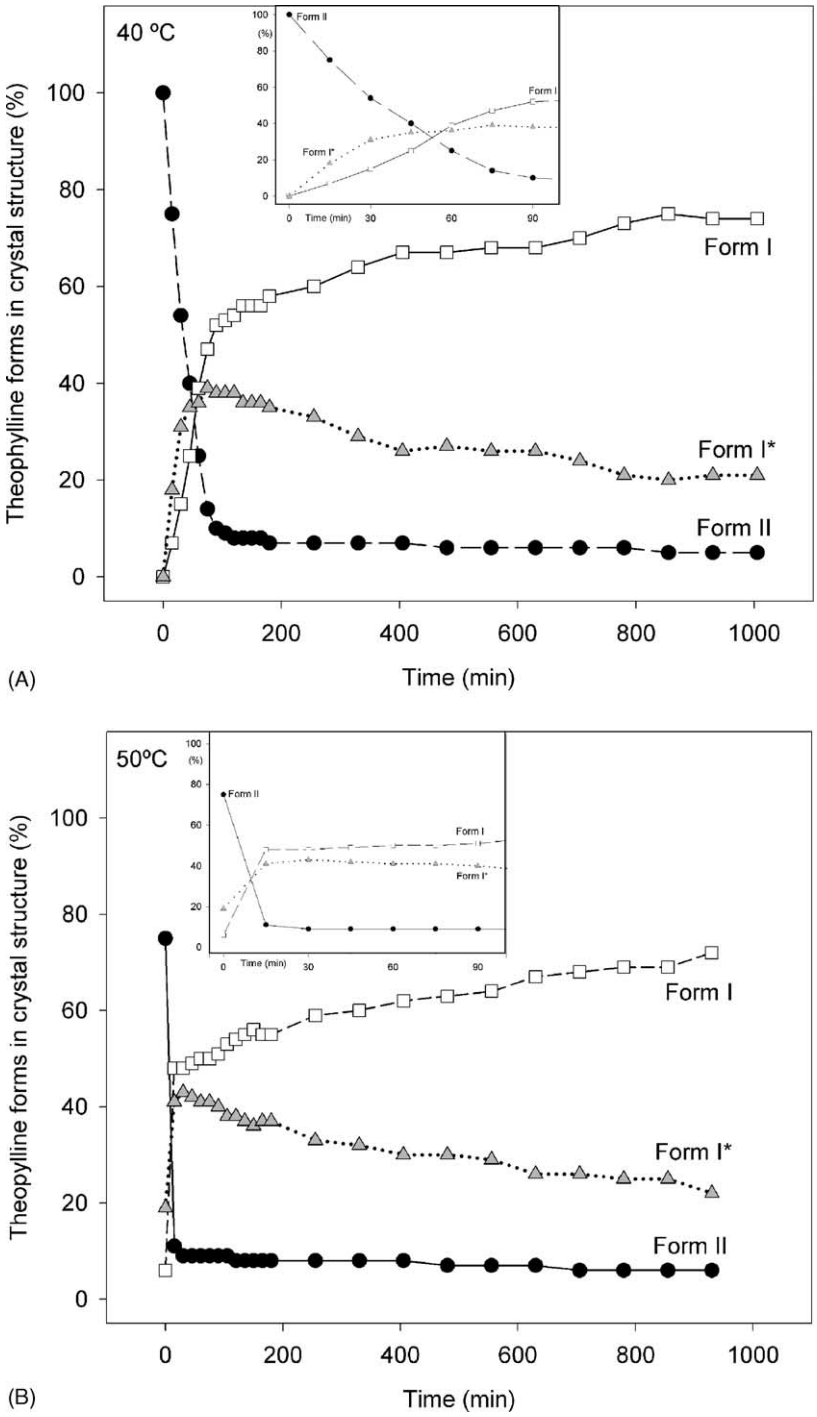

Fig. 3. The relative amounts of forms I, I* and II (monohydrate) in the crystal structure of theophylline granules dried (a) at 40 °C, (b) at 50 °C, (c) at 60 °C using a variable temperature-X-ray powder diffractometer (VT-XRPD).

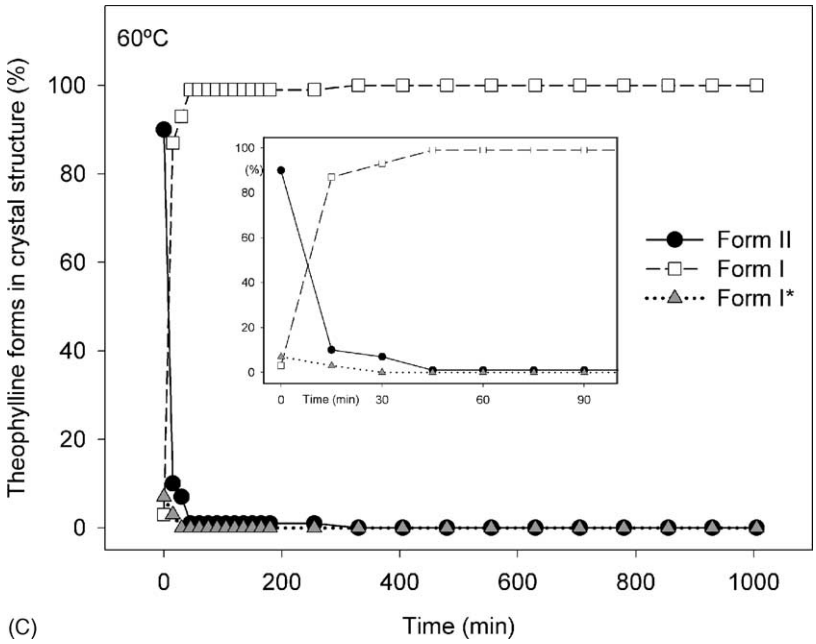

Fig. 3. (*Continued*).

granules dried in VT-XRPD the average crystallite size was 540 Å at drying temperatures 50–70 °C. In most cases, the final average crystallite size did not change after the first 15 min of drying at any temperature.

3.2.3. The effect of drying temperature and humidity on polymorphic transition

Wet theophylline granules consist of theophylline monohydrate (form II) and apparently free water molecules. During the drying process, theophylline monohydrate does not completely revert back to stable theophylline anhydrate (form I), since part of the anhydrate becomes a metastable form I*, as originally reported by Phadnis and Suryanarayanan (1997). Morris et al. (2001) suggested that fluid bed drying at low temperature favors metastable form of theophylline anhydrate (form I*). Our results show that of the three forms of theophylline metastable anhydrous theophylline was the major form between 40 and 50 °C with both drying techniques. Drying at temperatures over 50 °C produced mostly stable anhydrous theophylline (form I), which is consistent with previous findings by Morris et al. (2001). They suggested that a drying temperature below 60 °C and relatively low humidity ("fast" drying) would produce a metastable form of theophylline, whereas higher drying temperatures above 60 °C or interaction with moisture during drying ("slow" drying) would produce a stable form of theophylline. This differs from our finding that although drying temperatures above 50 °C produced mostly form I, humidity had only minor influence on the amount of form I* in the granules at these conditions when using an MMFD. Moreover, about 20–30% of form I* remained even after drying at 90 °C in MMFD under both humidity conditions. Drying at 40–50 °C using a VT-XRPD (under ambient conditions) the relative amount of form I* (40–45%) produced less than using an MMFD (70–65%, using ambient inlet air) at same conditions, and in addition the relative amount of 40–45% decreased to 20% after approximately 15-h drying time. The dehydration threshold temperature is the temperature at which 2% of the solvent (here water) is lost and this dehydration threshold temperature for theophylline hydrate is 47.3 °C (Perrier and Byrn, 1982). The threshold temperature of drying is related to the tunnel area, crystal packing, and perhaps also to defects within the crystal and the hydrogen-bond energy, which in turn is related to the length of the hydrogen bonds

(Byrn et al., 1999). Theophylline monohydrate is a slow-reacting hydrate with short and strong hydrogen bonds. This could explain why drying at temperatures 40–50 °C produced mostly metastable anhydrous theophylline especially during the fast drying process in the MMFD. To reduce the metastable form from dried theophylline granules, it seems that drying temperatures for theophylline monohydrate should be much higher than the dehydration threshold temperature of theophylline monohydrate.

When drying is done in an MMFD, the granules are in suspended hot air and the heat transfer is extremely rapid. Fluid bed granules usually have large porosity, which helps water to exit easily. In their studies of water tunnels in theophylline monohydrate, Perrier and Byrn (1982) have shown that the water chain has a zigzag pattern. If the tunnel is zigzag, the cross-sectional area may be too small and may not accurately reflect the size of the tunnel. Because the tunnels are relatively large, water can escape easily at the beginning of dehydration, but since the shape of tunnels is zigzag, the rest of water remains in the tunnel, and total drying consequently takes a longer time. Drying in an MMFD was done after the drying phase of normal fluid bed granulation and was stopped when the humidity of the inlet and outlet air were the same. The drying time of the granules varied depending on the drying temperature in the MMFD. As expected, higher drying temperatures led to shorter drying times. The drying process in the MMFD was monitored on the basis an apparent water absorbance (AWA) curve, which showed rapid evaporation of free water (heat transfer limited phase), followed by slower dehydration of monohydrate water molecules (mass transfer limited phase), and then stable AWA levels (Fig. 4). This is also consistent with the report of Wildfong et al. (2002). The kinetics of the drying process in the MMFD were monitored using in-line NIR spectroscopy (Rantanen et al., 2001; Räsänen et al., 2003). The decrease of free and hydrate water was indicated by a decrease in apparent water absorbance (AWA) during the drying process (Fig. 4). In the full NIR spectra, the water of crystallization of theophylline was detected as an absorption maximum at around 1970 nm, whereas the free water was detected as an absorption maximum at around 1900 nm. As expected, the drying rate increased at higher temperatures. At 80 and 90 °C, dehydration and drying kinetics were very similar under both inlet air humidity conditions (Fig. 4). A weak point of inflection was seen in the AWA curve (Fig. 4a), and the plateau in the curve (Fig. 4b) at the AWA level of 0.4 represents theophylline monohydrate. A plateau in the AWA curve is characteristic for the end of the drying process. The stable AWA value seemed to depend inversely on the drying temperature, but not on the moisture content of the inlet air, because using either dry or ambient inlet air resulted in qualitatively similar stable AWA levels at different temperatures. Stable AWA levels were somewhat higher at 80 and 90 °C than at 50 and 60 °C (Fig. 4), although the final dried granules had very similar moisture contents (Fig. 2). It is evident that this phenomenon reflects the formation of the metastable form of anhydrous theophylline (form I*), but increased triboelectrification of granules during drying may also influence the production of similar stable AWA levels.

3.3. Comparison of the effect of using two drying methods on polymorphic transitions of theophylline

Our results indicate that the highest relative amount of form I* in the crystal structure is generated after drying at 40 and 50 °C with both drying methods. With the present experimental setup using a fluid bed dryer (MMFD), we were unable to obtain form I alone without form I*. In contrast, drying in a VT-XRPD at 60 °C or above produced only form I already after the first 15 min.

In tray drying, the bed thickness, i.e. the mass of the granules, has a critical influence on drying (Carstensen and Zoglio, 1982). During drying in a VT-XRPD (simulated tray drying), the bed is fixed and the drying process is slower than when a MMFD is used, whereas during drying in a fluid bed, triboelectrification of powders may cause cohesion effects, the initial formation of agglomerates and adhesion to the wall of the container. Since in an MMFD the material is under higher mechanical attrition than in VT-XRPD during the drying process, we propose that differences in attrition that produce recrystallization may explain the differences we observed in form I* generation between VT-XRPD and the fluid bed dryers. Moreover increased triboelectrification of the granules during MMFD drying might result in a preferred orientation to the crystals. These effects are emphasized in microscale fluid bed drying, in which the amount of dried

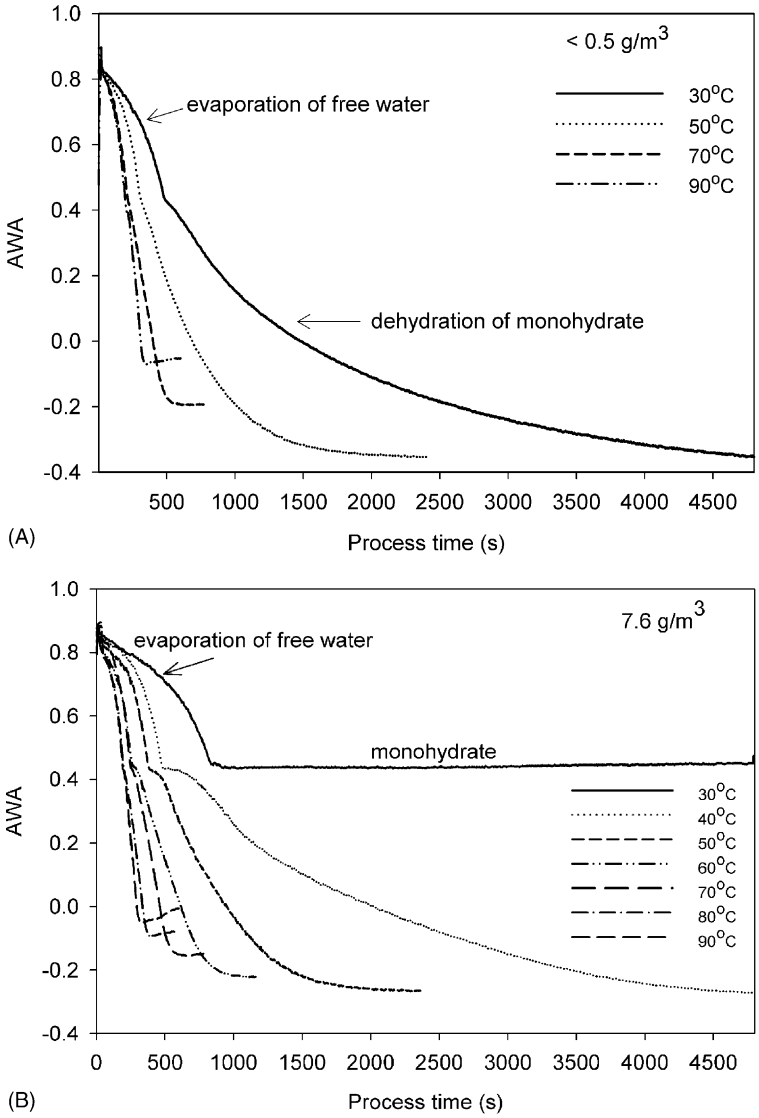

Fig. 4. Drying begins with rapid evaporation of free water followed by slower dehydration of monohydrate water molecules. Apparent water absorbance (AWA) values during drying in a multichamber microscale fluid bed dryer (MMFD) using temperatures ranging from 30 to 90 °C and (a) dry inlet air (under 0.5 g m^{-3}) or (b) ambient inlet air (7.6 g m^{-3}). The end of the drying process is characterized by a plateau in the AWA curve. Note the weak point of inflection in (a) and the plateau in (b) at an AWA level of 0.4, which represents theophylline monohydrate and the shift of different drying phases.

material is small and a larger proportion of the granules is in contact with the container wall than in a traditional fluid bed unit.

Our results show that drying in a fluid bed dryer produces greater relative amount of the metastable form of theophylline than drying in a VT-XRPD (simulated tray drying) under apparently similar temperature conditions and regardless of the humidity of the inlet air. Although the exact mechanism causing the difference in form I* generation between the two drying methods remains unclear, our findings raise the question whether fluid bed drying may produce higher amounts of an unstable polymorphic form than other drying methods, such as oven-drying. Another open question

is the effect of triboelectrification on polymorphism during the fluid bed processes.

Additional research is needed to determine the role of excipients in the formation of metastable forms during fluid bed drying. In practice, excipients are always present in the formulation during the drying phase both in fluid bed granulation and other drying processes. Since the excipients can have significant effects on the structure of theophylline (Airaksinen et al., 2003), it is possible that their presence may inhibit the formation of metastable forms in formulation during fluid bed drying.

4. Conclusions

Metastable anhydrous theophylline was the major form that was produced at drying temperatures of 40–50 °C with both MMFD and VT-XRPD drying techniques. Although drying at temperatures over 50 °C produced mostly stable anhydrous theophylline, over 20% metastable anhydrous theophylline remained even at 90 °C when drying in an MMFD. In contrast, drying the granules in a VT-XRPD produced only stable anhydrous theophylline after the first 15 min at 60 °C. We propose that differences in attrition that produce recrystallization may explain the differences in form I* generation between the two drying methods. Moreover, increased triboelectrification of the granules during MMFD drying may produce preferred orientation to the crystals. These effects are emphasized in microscale fluid bed drying, in which the amount of dried material is small and a larger proportion of the granules are in contact with the container wall than in a traditional fluid bed unit. These results indicate that using additional drying methods, including an MMFD, during the preformulation phase may be more informative about possible polymorphic transformations in the drug ingredients during the manufacturing process.

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