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Moisture induced polymorphic transition of mannitol and its morphological transformation

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Abstract

The effects of moisture on the polymorphic transition of crystalline mannitol were investigated. Mannitol has three polymorphic forms, and was classified as α, β, and δ form, respectively, by Walter-Lévy (C.R. Acad. Sc. Paris Ser. C (1968) 267, 1779). The water uptake of δ form crystalline was greater than that of the β form when each crystalline form was stored at 97%RH (25 °C). The different powder X-ray diffraction patterns obtained before and after humidification confirmed that a moisture induced polymorphic transition from the δ to β form had occurred. Morphological changes were also observed with an increase in the specific surface area of the δ sample from 0.4 to 2.3 m^2/g being found on exposure to humidity. Thus it was suggested that the observed higher hygroscopicity of the newly formed β form arose from the gradual increase in the surface area with the polymorphic transition from the δ to β form. When considering the mechanism of this polymorphic transition, the results from molecular modelling, cross-polarisation/magic angle spinning (CP/MAS) solid-state NMR spectra and scanning electron-micrographs suggest that water molecules act as a molecular loosener to facilitate conversion from δ to the β form as a result of multi-nucleation.

Keywords: Mannitol; Polymorphic transition; Moisture; Hydrogen-bonding; Morphological transformation

1. Introduction

Mannitol, a naturally occurring hexa-hydric alcohol, is commonly used as a pharmaceutical excipient for tablets due to excellent safety and compatibility with drugs (Kibbe, 2000). Mannitol is a particularly useful excipient when used with moisture sensitive drugs because of its non-hygroscopicity. Mannitol is also commonly used in the formulation of chewable tablets or rapidly disintegrating tablets in the oral cavity because of its negative heat of solution and thus cooling properties in the mouth.

Mannitol generally occurs as a crystalline excipient and several polymorphic forms are known to exist. Several reports on the solid-state properties of mannitol and its various forms can be found

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in the literature. For example, lattice parameters and infrared spectra were examined in detail by Walter-Lévy (1968), who concluded that three different polymorphs exist (namely α, β, and δ). Confirmatory findings were later reported by Berman et al. (1968), Jones and Lee (1970).

It is well known that conversion from one polymorphic form of a drug or excipient to another can be induced by heat, friction, grinding, tabletting, amongst other pharmaceutical procedures (Chan and Doelker, 1985; Matsumoto et al., 1991; De Villiers et al., 1991 Yu et al., 1998). Interestingly for mannitol, it has been noted that neither α, β or δ polymorphic forms undergo conversion on application of mechanochemical stresses, i.e. grinding and tabletting (Burger et al., 2000), despite the β form being the stable form under ambient conditions. Burger et al. (2000) also have investigated the relationships between the various forms highlighting the enantiotropic relationship between the β and δ forms and have recently confirmed results by Yoshinari et al. (2001) that show a moisture-mediated transition of δ to β occurs. Since mannitol is a commonly used excipient, which could encounter moisture during several formulation procedures, our aim is to present a detailed fundamental analysis of mannitol's moisture induced polymorphic transition. We also briefly consider the pharmaceutical benefits of this transition for solid dosage form design.

2. Materials and methods

2.1. Materials

The classification of mannitol polymorphs used is that according to Walter-Lévy (1968). Mannitol (β form) was the commercial product obtained from Merck (Darmstadt, Germany). Mannitol (δ form) was produced by recrystallisation from dilute aqueous acetone solution at below 0 °C, and washed with acetone rapidly to displace the water into acetone on the crystal surface. It is important to keep the temperature below 0 °C during the recrystallisation procedure to obtain the crystalline δ form and minimise the levels of β form, which has been detected in some batches using powder X-ray diffraction.

2.2. Scanning electron microscope (SEM)

Electron-micrographs of crystals were obtained using S-2300 (Hitachi, Tokyo, Japan) scanning microscope. The specimens were mounted on a metal stub with double-sided adhesive tapes and coated with gold under vacuum prior to observation.

2.3. Differential scanning calorimetry (DSC)

DSC traces of the samples were obtained on a Perkin–Elmer DSC7 differential scanning calorimeter connected to a Perkin–Elmer 7700 computer via the TAC7 microprocessor controller. PYRIS® software, was used to calculate extrapolated onset temperature, peak temperature and enthalpy values for each thermal event. The temperature axis was calibrated with pure indium, with a melting point of 156.60 °C and was checked using a zinc standard, with a melting point of 419.47 °C. Samples were scanned in an aluminium pan with a pin-holed lid. Sample mass (5–10 mg) and heating rate (5–60 °C/min) were varied according to the purpose of the experiments.

2.4. X-ray diffraction patterns (PXRD)

The powder X-ray diffraction patterns of the samples were obtained using a Siemens, Model D5000 diffractometer fitted with a scintillation counter and Cu Kα radiation source (wavelength = 0.15418 nm). The divergence and detector slits were of 0.3 and 0.18° aperture, respectively. Data were collected between 3 and 40° of 2-θ in a step mode using a step size of 0.02° of 2-θ and collecting time of 1 s per step. A temperature controlled cell was used to detect temperature dependent diffraction pattern changes.

2.5. FT-IR spectra

FT-IR spectra were recorded with FT-200 (Horiba, Tokyo, Japan). Samples were scanned as potassium bromide tablets at resolution of 2 cm^{-1} and 200 interferograms were accumulated for each spectrum.

2.6. Solid-state NMR

Cross-polarization/magic angle spinning (CP/MAS) 13C solid-state NMR spectra were obtained using a Varian Unity Plus spectrometer (Palo Alto, CA) operating at 75.43 MHz, with a Doty CP/MAS probe (Columbia, SC). The operating conditions were spectral width 30 kHz; relaxation delay 0.1 s; acquisition time 40.0 ms.

2.7. Moisture sorption experiment

The moisture sorption kinetics were determined using an automatic moisture balance (MB-100, VTI cop., Hialeah FL) and approximately 10 mg of sample. The balance was calibrated before each experiment, and the accuracy of percent relative humidity was periodically examined by determining the amount of moisture absorbed by Povidone K90 at 80% RH and 25 °C. For determination of the physicochemical properties of the moisture-exposed samples, a constant relative humidity chamber of 97%RH was prepared from a glass desiccator using a saturated solution of potassium nitrate (KNO_3).

3. Results and discussion

3.1. Confirmation of polymorphic form of the samples

Reference X-ray diffraction patterns for the three forms of mannitol were obtained (Fig. 1). The theoretical powder patterns were produced for the α and β forms using single crystal data and CERIUS software (Molecular Simulations, San Diego, CA). Since the single crystal structure of δ form is unknown, a reference powder X-ray diffraction pattern (Walter-Lévy, 1968) of the δ

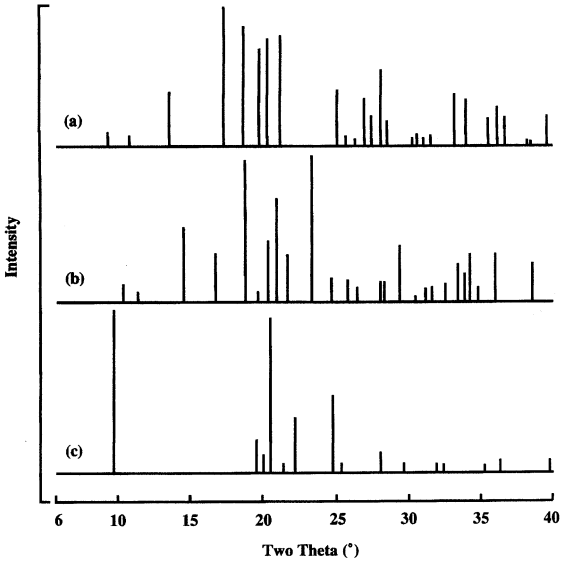

Fig. 1. Referential X-ray diffraction patterns of polymorphic forms of mannitol; (a) α form (b) β form, (c) δ form.

form is also included. The recrystallised sample was sieved to achieve the approximate same particle size as commercial products before its characterisation. It was found that the powder X-ray diffraction patterns of the commercial product and the recrystallised sample were β form and δ form, respectively, after comparison with theoretical or reference patterns (Fig. 2). On comparing diffraction patterns with the reference sample and the recrystallised sample, a difference in intensity between the patterns was attributed to minor

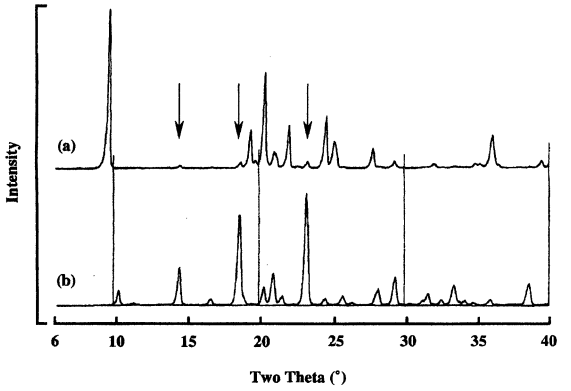

Fig. 2. X-ray diffraction patterns of mannitol samples; (a) recrystallised sample, (b) commercial product.

differences in the texture of the samples. The recrystallised sample contained a little amount of β form as identified by a diffraction peak (see arrow on figure). FT-IR spectra for their forms are shown in Fig. 3. Each of the forms displays a characteristic spectrum that compared well with the original analysis by Walter-Lévy (1968). The data confirm that commercial product and recrystallised sample are the β form and δ form, respectively. Significant spectral difference occurring in the region of 3700–2500 cm^{-1} suggested that variation in O–H or C–H stretching vibrations arises from the structural features of the forms. Differences in the DSC traces for the two forms also confirm the above polymorphic assignment. The DSC curve of the recrystallised sample has unique thermal events (Fig. 4). These are a small endothermic peak and an exothermal peak between 140 and 155 °C and then a relatively large endothermic peak at about 167 °C. However, the curve of the commercial product had a only melting peak at about 167 °C. To determine the reason for the observed thermal events between 140 and 155 °C, temperature controlled powder X-ray measurements were performed. The diffraction patterns resulting from these studies are shown in Fig. 5. A change in the pattern occurs when the sample temperature was elevated from 30 to 155 °C. The first small endothermic peak was identified as a melt and the following exothermal peak was shown to be solidification to the β form, indicating that the β form was the stable form and that the δ form was meta-stable at around 155 °C.

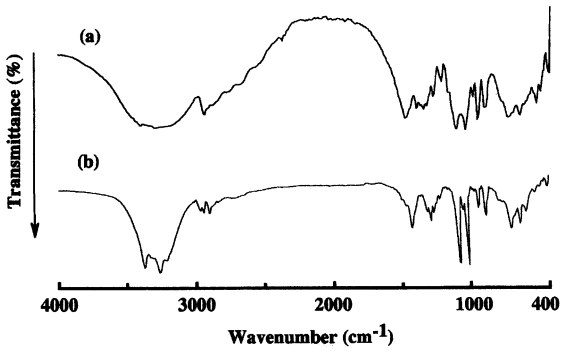

Fig. 3. FT-IR spectra of mannitol samples; (a) recrystallised sample, (b) commercial product.

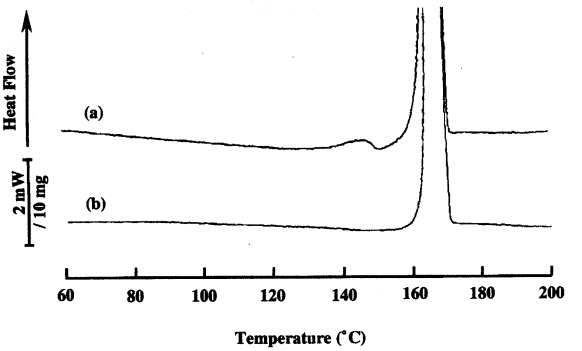

Fig. 4. DSC traces of mannitol samples; (a) recrystallised sample, (b) commercial product.

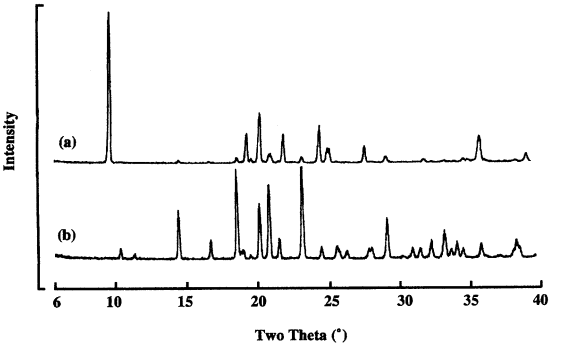

Fig. 5. Temperature controlled powder X-ray measurement of the recrystallised sample; (a) 30 °C, (b) 155 °C.

Burger et al. (2000) reported in detail the thermal relationship between β and δ forms, and they concluded that this relationship was enantiotropic, with a transition temperature between absolute 0 and 403 K. The commercial product and recrystallised sample are named β-crystal and δ-crystal, respectively, in the following studies and physicochemical data for the two samples are summarised in Table 1.

3.2. Moisture sorption characteristics and polymorphic transition

The moisture sorption characteristics of the polymorphic forms were compared using weight change against time data that are presented in Fig. 6. On exposure to 97%RH, 25 °C, both samples started to absorb moisture after a lag time of

Table 1
Physicochemical data for two mannitol samples

	β-Crystal	δ-Crystal
Polymorphic form	β	δ
Melting point (°C)	167	>155
Polymorphic transition by heat	–	Into β form
Mean particle size (μm)[a]	22.85	28.12
Specific surface area (m^2/g)[b]	0.5	0.4

[a] Laser diffraction method.
[b] BET method.

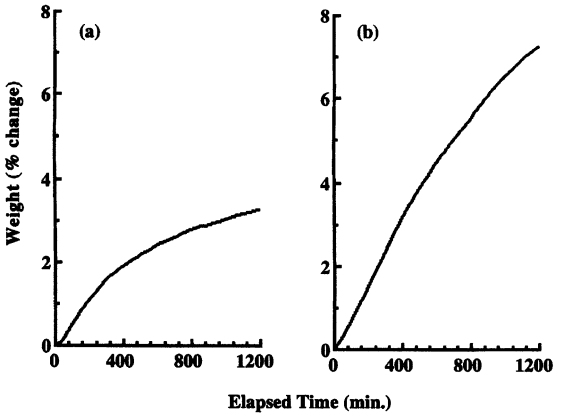

Fig. 6. Comparison of moisture adsorption profiles among mannitol samples, exposed to 97%RH, 25 °C; (a) β-crystal, (b) δ-crystal.

about 30 min. The rate of moisture absorption of δ-crystal was much greater than that of β-crystal, and the total amounts absorbed after 20 h were 7.2 and 3.2% w/w, respectively. Umprayn and Mendes (1987) studied the moisture absorption of cefaclor and reported that the adsorption curves could be described by:

$$W_t - W_0 = kt^{1/2}$$

where W_t and W_0 are the total and initial weight of sample at time t and 0, respectively; k is the rate of moisture uptake. The weight change of the two polymorphic forms against square time was shown in Fig. 7 and also presented is data for the re-exposure of the δ-crystal to moisture after the initially exposed material had been vacuum dried. It can be seen that the rate of moisture absorption of β-crystal was relatively constant in comparison

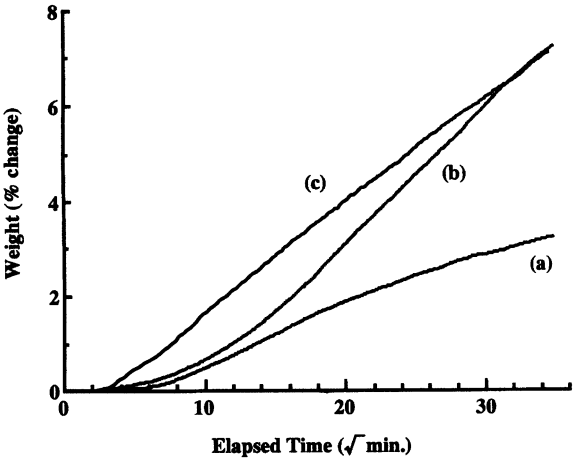

Fig. 7. The weight change of mannitol samples against square exposure time; (a) β-crystal, (b) δ-crystal, (c) re-exposure of δ-crystal.

with the data obtained for the δ-crystal, whose rate of sorption accelerated with time. After vacuum drying of the moisture-absorbed sample of δ-crystal, the resorption profile was also almost linear. This suggests that an irreversible physical change occurred during the moisture sorption test for δ-crystal. Surprisingly the rate constant for the resorption sample of δ-crystal was about 2.2 times higher than that of the β-crystal, despite the initial specific surface area of the two forms being very similar (Table 1). A powder X-ray diffraction pattern was obtained on storing δ-crystal in a desiccator (97%RH, 25 °C) overnight and this is shown in Fig. 8. The diffraction pattern agreed well with the pattern obtained for the reference β form. Thus moisture vapour is able to bring about a transition of the δ form to the β form.

3.3. The mechanisms of polymorphic transition

To fully understand the mechanism of polymorphic transition from δ to β form, single crystal diffraction structures would provide important structural information at the molecular level. Such molecular modelling information exists for the β form of mannitol (Fig. 9) whose lattice parameters are $a = 8.694$, $b = 16.902$, $c = 5.549$ Å, respectively. It can be seen that each oxygen is both a hydrogen bond acceptor and a hydrogen

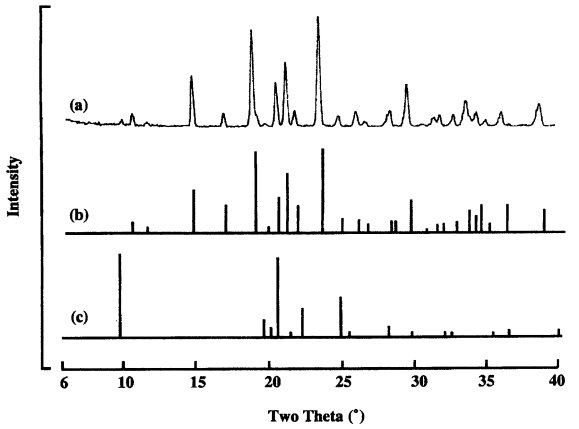

Fig. 8. Powder X-ray diffraction pattern of the exposed δ-crystal to 97%RH for overnight; (a) exposed sample, and reference pattern of (b) β form, (c) δ form.

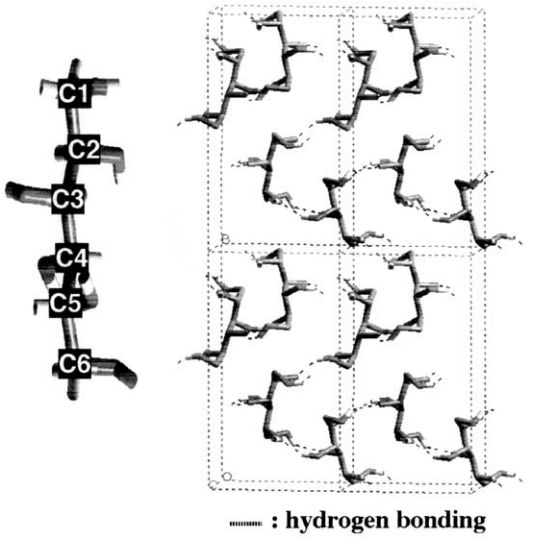

Fig. 9. Molecular and unit cell structure of β form of mannitol.

bond donor. Similarly the structure reveals that the oxygen bonded C1 and C6 carbons interact with either the oxygen bonded C5 and C2 carbons, or the oxygen C3 and C4 carbons. Thus C1 and C6 carbons have two different structural environments. Unfortunately, the crystal structure of the δ form has not been solved. In the absence of such data, Solid-state NMR may be able to offer some insight into the structural differences between the two forms. Grindley et al. (1990) reported that ^{13}C-Solid-State NMR spectra of polymorphic mannitol forms gave distinctly different chemical shifts that can be used for polymorphic characterisation. The ^{13}C-NMR spectra we present are shown in Fig. 10. The spectrum of δ-crystal on exposure to 97%RH best conforms to the spectrum of the β form and thus supports our finding that a polymorphic transition occurred on exposure to elevated humidity. Comparing the spectrum with the δ form and β form, the most significant differences occur in the C1 and C6 carbon environments. The chemical shift of C1and C6 carbon of δ form and β form were 64.4, 64.4 and 64.3, 62.8 ppm, respectively. The results indicate that these carbons, situated at either end of the mannitol backbone, have near-equivalent environments for the δ form, and differ from the β form as previously discussed.

To estimate solvent dependency of this polymorphic conversion, a physical mixture of β-crystal and δ-crystal (50/50% w/w) was suspended in various solvents under ambient conditions and the composition of the suspension analysed with time. The resulting data are summarised in Table 2. In the cases of water and ethanol, the mixture rapidly converts to β form within a day. Despite

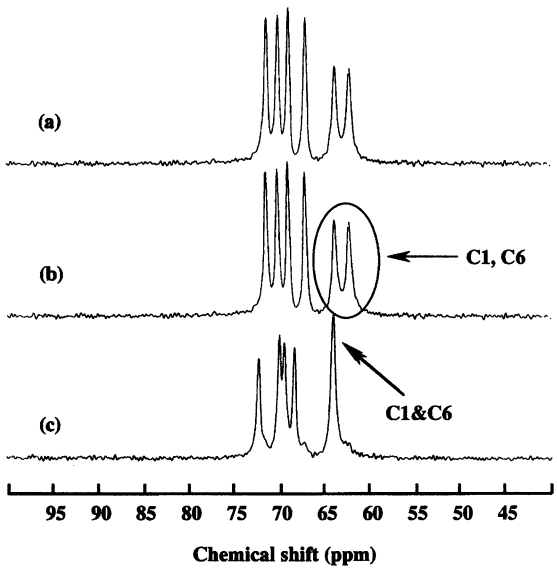

Fig. 10. ^{13}C solid-state NMR spectrum of the exposed δ-crystal to 97%RH for overnight; (a) exposed sample, and reference spectra of (b) β form, (c) δ form.

Table 2
Solvent dependency of polymorphic conversion

Solvent	Percent ratio of β form	Time	Solubility (w/w%)[a]
Water	100	Within a day	20
Ethanol	100	Within a day	0.01
Acetone	50 (no change)	Over 6 month	0.01

[a] Solubility of β form crystalline at 25 °C.

the solubility of mannitol in acetone being almost identical to that of mannitol in ethanol, no change in the composition of the suspension in acetone could be detected up to 6 months. A possible explanation for this difference in the ability of ethanol and acetone to induce polymorphic transition could lie in their ability to interact with mannitol's lattice structure. It was surmised that solvents containing a hydroxyl group were able to alter the hydrogen-bonding networks of solid-state mannitol. Solid-state NMR relaxation data of the polymorphic forms were obtained in order to estimate the molecular mobility characteristics of each structure. The obtained spin-lattice relaxation (H1/s) times are summarised in Table 3. From this proton data, the relaxation time of δ-crystal was about twice as long as that of the β-crystal. In contrast to proton data, for carbon, relaxation times for δ-crystal were around half that of the times obtained for the β-crystal. Such findings are consistent with the δ-crystal structure being composed of a loose carbon-backbone and a rigidly linked hydrogen bond network, as compared with β-crystal. The tightly established hydrogen-bonding network of the δ form would act to protect against conversion to the β form on ambient storage or during a mechanochemical procedure. However, in the presence of solvents with hydroxyl groups, the intra- and inter molecular hydrogen-bonding of the δ form interacts with the solvent hydroxyl group and crystal form conversion is able to occur as a result of hydrogen bonds being broken. Thus such a solvent molecule acts as molecular loosener to facilitate conversion.

3.4. The morphological transition

Scanning electron microscope (SEM) images of the moisture-exposed samples were observed and are shown in Figs. 11 and 12. In the case of β-crystal, there are no significant differences between the samples before and after exposure to 97%RH and 25 °C for 20 h. On the other hand, the on exposure of the sample of δ-crystal a change to a smaller primary particle size was readily apparent on conversion from the δ to β form. This morphological change was considered to be brought about by water molecules acting to disrupt the hydrogen bonds of mannitol at multiple sites and to be followed by the immediate reconstruction of a hydrogen network to of the newly established thermodynamically stable crystal (β form). This hypothesis is consistent with the further finding that the specific surface area also changed from 0.4 to 2.3 m^2/g when the δ form of mannitol was exposed to moisture and converted to the β form as a result of multi-nucleation. It was

Table 3
Solid-state NMR relaxation time of polymorphic mannitol samples

Form	Signal/ppm	62.4	64.0	67.2	62.4	70.2	71.5	Average
β	T1 (H)/s[a]	210	236	231	228	227	222	226
	T1 (C)/s[b]	2190	2680	3360	3230	3210	3110	2963
		64.2	68.4	69.6	70.0	72.3		Average
δ	T1 (H)/s[a]	457	488	451	448	458		460
	T1 (C)/s	1030	1780	1750	1700	1670		1586

[a] Spin-lattice relaxation time of proton and carbon.
[b] Spin-lattice relaxation time of proton and carbon.

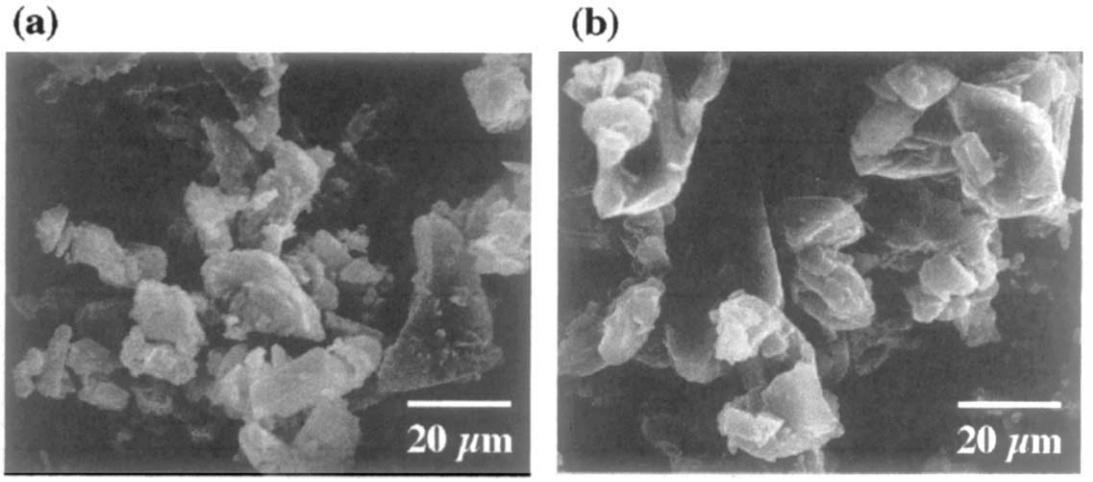

Fig. 11. Scanning electron-micrographs of β-crystal; (a) as received, (b) after exposure to 97%RH for 20 h.

concluded that the observed hygroscopic difference between β-crystal and δ-crystal was influenced by the increase in the specific surface area of the solid during polymorphic conversion.

4. Conclusion

The polymorphic transition from δ to β form was triggered by moisture with a consequent morphological change bringing about an almost 6-fold increase in surface area. Formulators need to anticipate such changes such as this polymorphic transition because this morphological change was also observed to occur during a wet granulation process and could be commonplace. To date there are no polymorphic specifications in any pharmacopoeias concerning this transition. The formulation consequences of this polymorphic transition for pharmaceutical performance including compressibility are under investigation.

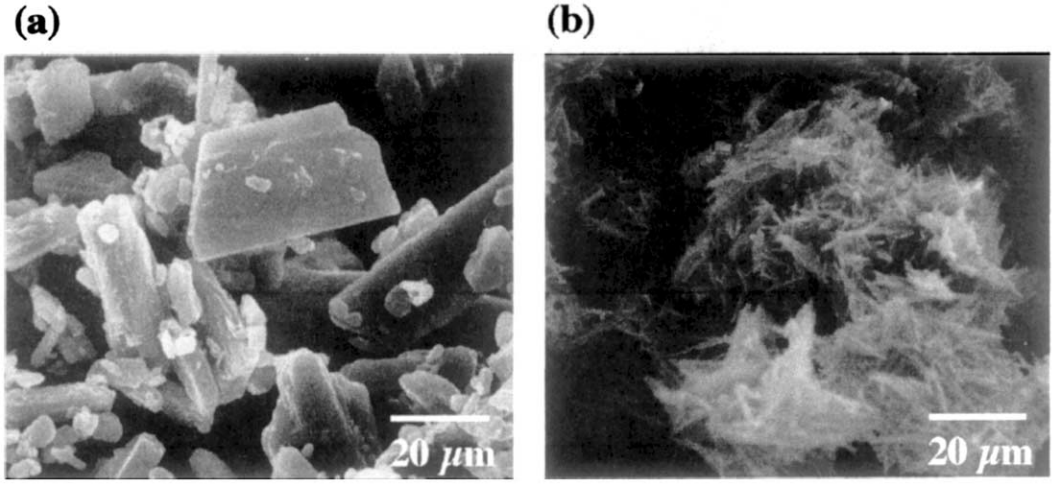

Fig. 12. Scanning electron-micrographs of δ-crystal; (a) before, (b) after exposure to 97%RH for 20 h.

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