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Stability of polymorphic forms of ranitidine hydrochloride

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Ranitidine-HCl can exist in two different polymorphic forms: form I (m.p. 134–140 °C) and form II (m.p. 140–144 °C). In the present study the stability of form I of ranitidine-HCl to a selection of powder pretreatments, to reflect conditions which might occur in manufacturing procedures, and also to a limited range of storage conditions was investigated. The original samples of form I and form II used were characterised by X-ray powder diffraction (XRPD), hot stage microscopy (HSM) and differential scanning calorimetry (DSC). A quantitative XRPD method for determining the fraction of form II in the presence of form I was used. XRPD data were analysed using regression techniques and artificial neural networks (ANN). The quantitative XRPD technique was then used to monitor the relative proportion of form II in each treated sample. Pretreatments of form I included (i) mixing with form II or with common excipients (ii) compression and grinding (iii) contact with solvents (followed by drying) before storage. Storage conditions involved three temperatures (20 °C, 30 °C, 42 °C) and three relative humidities (45% RH; 55% RH; 75% RH). Samples were stored for a period of 6 months. A limited factorial design was used. No increase in the form II:form I ratio was observed in the following pretreatment processes: introduction of form II nuclei into form I; introduction of excipients to form I; compression of form I powder at 5 and 15 tons; normal mixing and grinding processes; addition of isopropanol (IPA) or water/IPA mix followed by drying. In the pretreatment process where water was added to form I powder (with most or all of the powder dissolving), drying of the liquefied mass led to a mix of form I and form II. On storage at room temperature (20–30 °C), low relative humidity (45–55% RH), and in an air-tight container there was no increase in the form II:form I ratio. Storage of form I/form II mixes, particularly at high humidity, resulted in a preferential loss of form II (compared to form I). Loss was greater at 30 °C/75% RH than at 20 °C/75% RH. Form II was also preferentially lost under low humidity conditions created by a saturated solution of potassium carbonate (45% RH) at the elevated temperature of 42 °C. This environment was shown to be acidic.

1. Introduction

Polymorphism of drugs has been shown to be an extremely important factor for the quality of pharmaceutical products. Different polymorphic forms of a drug may have different solubilities and dissolution rates. In some situations, even the bioavailability of a product is influenced by the polymorph present in the formulation. It is important that the desired polymorph is present throughout the manufacturing process and also during storage of the product and does not transform to another polymorph (or pseudopolymorph) with different solubility/dissolution characteristics.

Ranitidine-HCl is reported to exist in two polymorphic forms (I and II). The melting point of form II (140 to 144 °C) is slightly higher than that of form I (134 to 140 °C) [1, 2]. If the polymorphs are monotropic this would suggest that form I would be metastable and form II stable. The polymorphs may, however, be enantiotropic. Carstensen and Franchini (1995) were unable to demonstrate transformation of form I to form II (or vice versa) in their studies [2] and were unable to conclude whether the polymorphs were enantiotropic or monotropic. They could, however, show that equilibrium solubilities were very similar (although the solubility of form II was unexpectedly slightly higher than that of form I since often melting point and solubility are correlated).

The aim of this study was to investigate the stability of form I of ranitidine-HCl to a selection of powder pretreatments, to reflect conditions which might occur in manufacturing procedures, and also to a limited range of storage conditions. X-ray powder diffraction (XRPD) was used to monitor the form II/form I ratio. Pretreatments of form I reported here included (i) mixing with form II or with common excipients (ii) compression and grinding (iii) contact with solvents (followed by drying) before storage. Storage conditions involved three temperatures (20 °C, 30 °C, 42 °C) and three humidities (45% RH; 55% RH; 75% RH). Samples were stored for a period of 6 months. A limited factorial design was used.

2. Investigations and results

The characterisation (via XRPD, HSM, DSC) of the original powders showed that they were polymorphic forms I and II of ranitidine-HCl (as recorded in Powder Data Files of JCPDS (1996) and also Zantac Patent Documentation (1995)) without solvent stoichiometrically entrapped [3]. Fig. 1 shows the diffractograms of the two polymorphic forms of ranitidine-HCl. Form I has three distinctive peaks (F1(1), F1(2) and F1(3) while form II has two distinctive peaks (F2(1) and F2(2)). Elemental analysis corresponded well to the theoretical composition of true polymorphic forms of ranitidine-HCl: Carbon = 44.7%, hydrogen = 6.5%, nitrogen = 16.1%; sulfur = 9.1%. SEM reveals the primary and secondary particle size of the initial form I and II powders (Fig. 2). The melting points (HSM, 1 K/min heating rate) of the two forms were within the range of quoted literature values, with Form I melting at 138 °C (literature value: 134–140 °C) and Form II melting at 140 °C (literature value: 140–144 °C) [1, 2].

After mixing (form I with form II or form I with the excipients microcrystalline cellulose, vinylpyrrolidone-vinylacetate-copolymer, and magnesium stearate) and after compression (form I) no change in form II/form I ratio (which could reflect form I to form II transformation) occurred in any of the samples. Also after addition of isopropanol or a mix of isopropanol and water followed by drying no change in polymorph composition could be detected. The characteristic peaks of form II were not detected in samples of form I after pretreatment, nor did the fraction of form II (with respect to form I) increase in the samples into which form II had been introduced. However in the samples of form I that were pretreated with pure water the recovered samples (before storage) contained a mix of form I and form II. The XRPD showed the distinctive peaks of form II and the proportion of form II was on average about 24%.

Control samples, stored in the absence of moisture, showed no change in the 6 month storage period. However, some of those stored in the presence of moisture

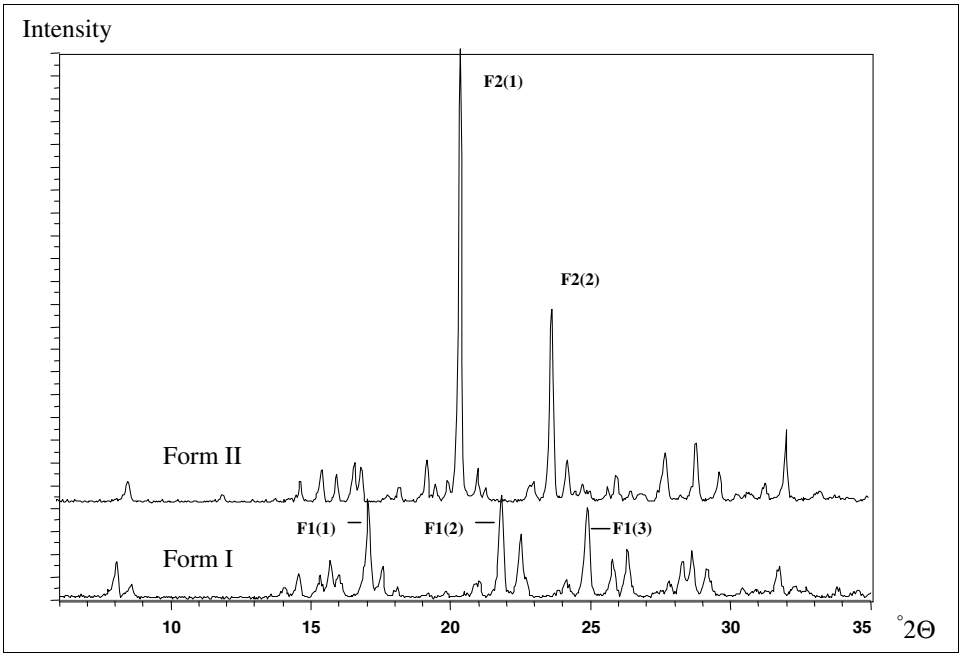

Fig. 1:
X-ray diffractograms of ranitidine-HCl form I and form II. F1(1), F1(2), F1(3) and F2(1), F2(2) are the distinctive peaks of Form I and Form II respectively

showed significant change as outlined below. The Table summarises these findings.

No change in appearance was detected in any samples stored at 20 °C/45% RH, 20 °C/55% RH, or 30 °C/55% RH or in the control samples. Discolouration occurred in the samples stored at elevated temperatures: 30 °C/45% RH, 30 °C/75% RH, and 42 °C/45% RH. Powders turned yellow-brownish gradually. At the lower humidity (45% RH), the brownish coloration only appeared on the top layer of the powdered samples and samples appeared dry. At 75% RH the powdered samples stored at 30 °C absorbed significant quantities of moisture, shrank and turned yellow-brownish gradually. Some of these samples liquefied totally, as a result of dissolution.

Form I alone (powder – no pretreatment): Very little moisture uptake occurred at 45% RH or 55% RH; slow uptake occurred at 20 °C/75% RH (less than 1% weight gain in 6 months – linear increase); fast uptake occurred at 30 °C/75% RH (27% weight gain in 6 months – linear increase). Samples stored at 75% RH gradually liquefied (with dissolution of the solid) as moisture uptake occurred. Diffraction patterns of the samples (including pastes obtained from some samples stored at 30 °C/75% RH) indicated presence of form I only; liquefied samples (obtained after some months at 30 °C/75% RH) that were dried at room temperature in a vacuum desiccator, were also found to consist only of form I. Although decomposition had occurred in these liquefied samples no other peaks appeared in the diffractogram, indicating decomposition products were not crystalline and/or were only present in minor quantities.

Form I with excipients: Moisture uptake was only seen at 75% RH (much greater at 30 °C (24% in 6 months-non-linear increase) than at 20 °C (14% in 6 months-non-linear increase); XRPD of powders, pastes and redried samples showed only form I to be present. Moisture uptake occurred more quickly initially in the presence of the excipients but % uptake over the full 6-month period did not exceed that obtained with pure drug.

Form I with form II: Only samples stored at 75% RH showed moisture uptake, which was again much faster at 30 °C (28% in 6 months – linear increase) than at 20 °C (less than 1% increase in 6 months). XRPD on samples, including pastes (30 °C/75% RH) and dried pastes of the 50 : 50 form I/form II mix showed progressive preferential loss of form II from the samples (Fig. 3). XRPD of the 99 : 1 form I : form II mix was not conclusive due to lack of sensitivity of the analytical technique. However, no marked increase in the

Table: Stability of ranitidine-HCl samples, pretreatments and storage conditions

Sample & pretreatment	20 °C 45% RH	30 °C 45% RH	42 °C 45% RH	20 °C 55% RH	30 °C 55% RH	42 °C 55% RH	20 °C 75% RH	30 °C 75% RH
Loose powders								
form I	×○	Δ○	Δ○	×○	×○	×○	Δ§○	Δ*
form I plus excipients	×○	Δ○	Δ○	×○			Δ§○	Δ*
form I : form II (50 : 50)	×○	Δ○	Δ➲	×○			Δ§➲	Δ*➲
form I : form II (99 : 1)	×○	Δ ?	Δ ?	×○			Δ§ ?	Δ* ?
Compression								
form I – 30	×○							Δ○
form I – 100	×○							Δ○
Solvent pretreatment								
form I – IPA	×○				×○			§○
form I – IPA:water	×○				×○			§○
form I – water	×➲				×➲			§Δ➲

× no visible changes
Δ visible decomposition
§ moisture uptake and shrinking
* sample liquefied
○ XRPD does not show increase in proportion of form II
➲ XRPD changes in ratios of form II to form I
? lack of XRPD assay sensitivity
empty cells – conditions have not been studied

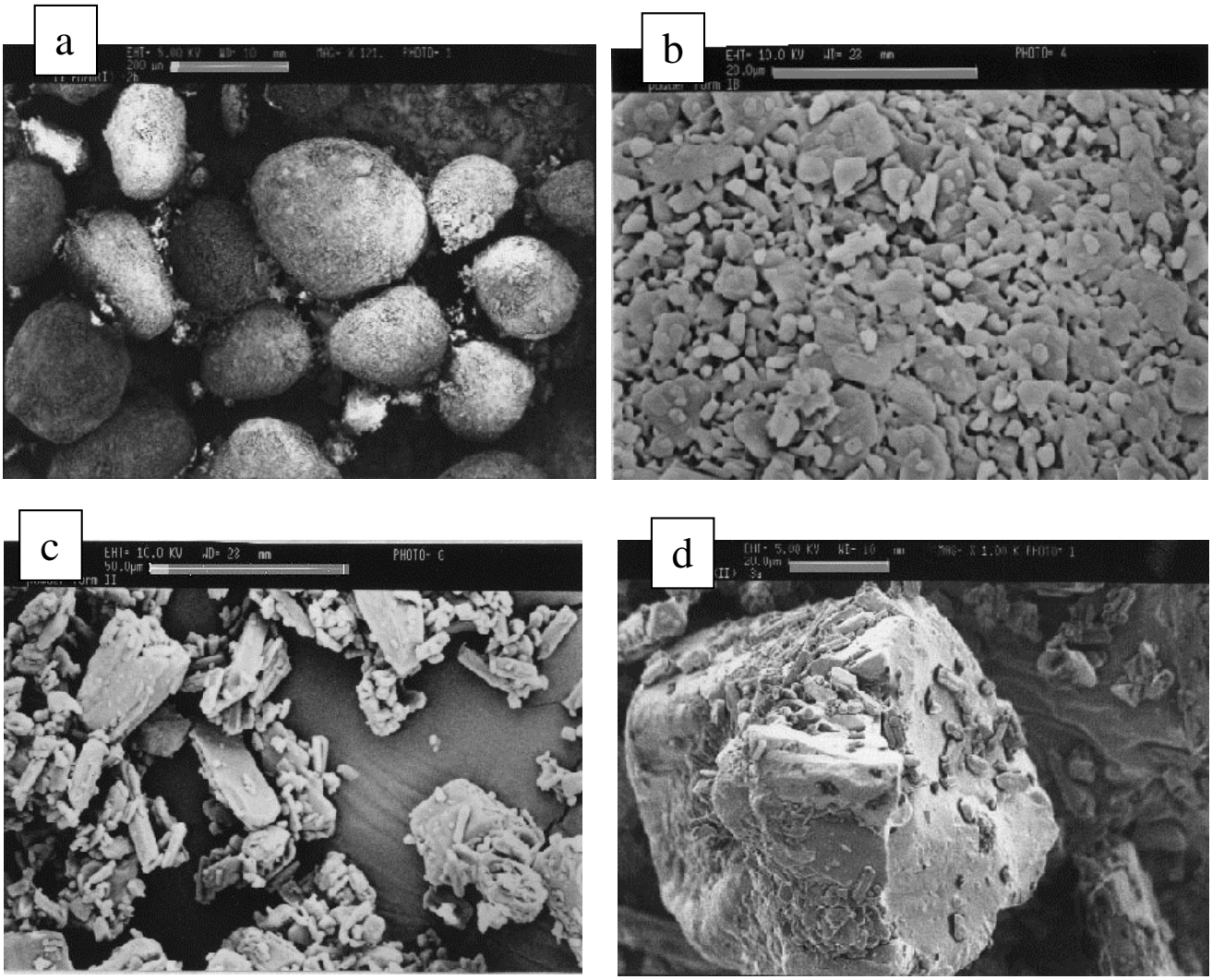

Fig. 2: Scanning electron micrographs of powder samples of ranitidine-HCl form I (a, b) and form II (c, d). Bar: a = 200 μm, b = 20 μm, c = 50 μm, d = 20 μm

heights of the distinctive peaks of form II (F2(1) and F2(2)) compared with those for form I was seen.

Form I compressed at two pressures: These samples were stored in compressed form as laminated pieces. Little moisture uptake occurred even at 75% RH. XRPD showed no detectable form II in the samples.

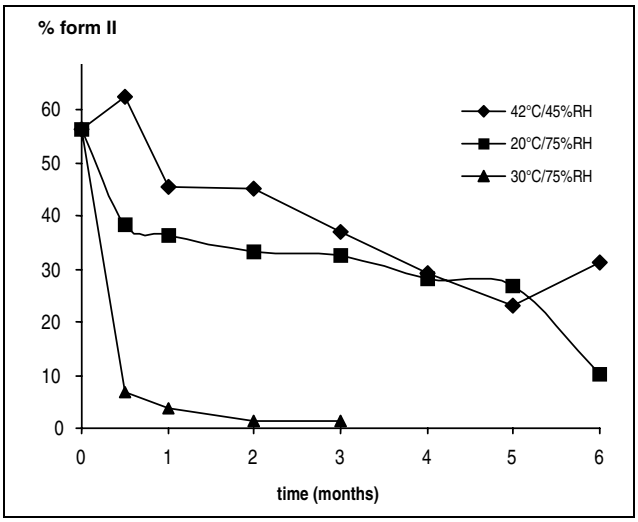

Fig. 3: Weight% of ranitidine-HCl form II remaining in 50 : 50 form I/form II samples on storage under different conditions

Form I subjected to solvent pretreatment and drying: After recovery from pretreatment, samples which had been exposed to water were shown to be a mix of form I and form II. The sample compositions varied from batch to batch; with an average of 24% form II. On storage, this powdered mix absorbed moisture at 75% RH and XRPD showed preferential loss of form II from the mix. Samples stored at 55% RH and 45% RH also showed preferential loss of form II. Loss of form II at 45% RH (42 °C) was faster than from 55% RH (30 °C). Other solvent pretreatment samples (mixed with IPA and with IPA/water mix) showed no formation of form II or increase in form II proportion upon storage.

3. Discussion

XRPD was used for both qualitative and quantitative purposes in this study and the quantitative technique [6] had been shown to be effective for determining form II in the presence of form I at form II levels as low as 1%. Analysis of the two forms of ranitidine-HCl was possible, even in the presence of large amounts of excipients. However, the technique was not sufficiently sensitive to quantify amounts of form II in the 0 to 1% range. No other significant peaks appeared in the diffractograms indicating no significant change to other crystalline products. Although some samples showed decomposition (as reflected by

brown discolouration) the extent of decomposition in the pretreated and in the stored samples was not quantified. The presence of the known decomposition products (including molecular adducts, outlined by Teraoka et al.) was not considered likely to selectively change the stability of one polymorph compared to the other [4].

Whilst upon storage no conversion of form I to form II (increase in form II/form I ratio) could be detected, pretreatment of form I with water (followed by drying) resulted in the formation of a mixture of form I and form II from the original form I powder. The solid dissolved on pretreatment and during drying a "glassy" product resulted. The glassy product was obtained both via repeated freeze-drying of the product and also when most of the water was removed using a rotary evaporator at moderate temperature. However, sample pretreated with a mix of water/IPA showed no form II, perhaps because a significant amount of the form I powder remained undissolved and these crystals acted as nuclei to direct the recrystallisation of the ranitidine-HCl which had dissolved, while the samples (from water pretreatment), in which form II was formed, were possibly in a completely amorphous state prior to recrystallisation. Since Carstensen and Franchini [2] have reported that the two polymorphs have fairly similar properties and described them as "isoenergetic polymorphs", both forms may crystallise together from the amorphous state when subjected to repeated shock cooling/storage at low temperature. It is possible that the duration and extent of the cooling process was also important and not just the state of the system at the time of cooling. To investigate this further it would be necessary to expose other samples (with a range of solvent pretreatment conditions) for various time periods to extremely low temperatures.

No storage condition in the present study resulted in a detectable transformation of form I to form II. Some storage conditions, on the other hand, resulted in a preferential loss of form II from powders containing both form I and form II. However, exposure to moisture and/or acidic atmosphere was necessary for this to occur. Usually, the greater the RH and the higher the temperature, the faster the rate.

Since loss of form II occurred preferentially to loss of form I (form II/form I ratio decreased) from the form I/form II mixes, regardless of whether they were physical mixes prepared from separate polymorphic forms or mixes prepared *in situ* (via a pretreatment process) it can be concluded that the preferential loss of form II cannot be a result of different crystal size, since the forms in the solvent-recovered samples would have had identical crystal size. Differences observed may thus be due to other factors. Since there was some, but not always much moisture uptake and also brown discolouration (decomposition), it could be suggested that form II is either preferentially dissolving (which is however unlikely, since equilibrium solubilities are reported as very similar [2]), or it is preferentially decomposing. It is also possible that a polymorphic transformation of form II to form I occurs with both decomposition and dissolution of both polymorphs at the same time and at a similar rate. The conditions of temperature and solvent (under which the partially or completely liquefied samples are dried) may also determine the polymorphic form which is obtained. In samples stored at 45% RH (in which change occurred) little moisture was present, while at 75% RH samples became progressively liquefied (with dissolution of solid). A much greater level of drying was thus required for the 75% RH samples. Teraoka et al. [4] have suggested that moisture below the critical relative humidity (CRH) is present as water molecules adsorbed onto the crystal surface whereas above the CRH the powder liquefies. The processes at 45% RH and at 75% RH could thus be slightly different.

Interestingly, XRPD signals of form I did not appear to increase in intensity, while the form II peaks decreased in intensity. So the possibility of conversion of form II (and perhaps also some form I) to an amorphous form of ranitidine (ie. loss of crystallinity) after contact with moisture and drying cannot be excluded but it was not possible to provide experimental evidence to support or disprove this hypothesis via analysis of DSC thermograms since ranitidine-HCl decomposes upon melting. However, even if amorphous material was being formed via a liquefaction (dissolution) and drying process, it is unusual that the ratio of form II/form I is decreasing with storage time and in some conditions form II appears to disappear completely. No new diffraction peaks were seen so appearance of significant amounts of a third polymorph or a pseudopolymorph (hydrate) or crystalline decomposition products can be excluded. A loss in crystallinity, after contact with water, was previously reported by Carstensen and Franchini [2].

Unpredictably, samples stored at 42 °C/45% RH turned brown faster than other samples and resulted in a preferential loss of form II faster than expected. The humidity (45% RH) was much lower than the CRH [4, 5] and thus very little moisture uptake occurred, yet significant loss of form II was found to occur. A saturated solution of potassium carbonate was used for humidity control. This solution created a slightly acidic environment in the storage box. Ranitidine-HCl is less stable in acidic conditions than in neutral pH conditions [4]. The relationship between the acidic nature of the environment, brown discolouration, decomposition and the preferential loss of form II however, needs to be further investigated.

Since this stability study only included a limited number of storage conditions, a fuller range of storage conditions plus storage and sampling of some systems for a very much longer period of time would be desirable to more fully define the process of form II loss from the system. Quantitation of the decomposition products should also be carried out and the role of these products in the change in form II/form I ratio with storage evaluated.

The initial hypothesis that form I (with lower melting point) might be metastable and convert to form II (with higher melting point) was not supported by the findings reported in this paper. It is thus possible that the polymorphs may be enantiotropic, so that under some conditions form II is able to convert to form I (thus explaining the decrease in the form II/form I ratio). However, the possibility of a preferential loss of form II compared to form I by dissolution and/or decomposition must also be considered.

In conclusion, as the "preferential loss of form II" was only identified after storage in the presence of moisture (under which conditions ranitidine-HCl of both forms is readily soluble) so that dissolution/recrystallisation may occur at the crystal surface (particularly when drying occurs after removal from storage) it is likely that the conditions of drying/recrystallisation play some role in directing the polymorphic form. Polymorph transformation (with decrease in form II/form I ratio) may therefore occur via a dissolution/recrystallisation process where the polymorph recrystallisation may be influenced by nuclei present, the changing environment (moist/acidic) and temperature. The form II/form I ratio did not change in the absence of moisture at 20 °C to 42 °C, as shown by the stability of the samples kept in air-tight containers.

4. Experimental

4.1. Materials

Polymorphic form I (Lot CH-B560018) and II (Lot A-Nr 32005) of ranitidine-HCl were provided by Dolorgiet AG, St. Augustin, Germany; isopropanol (IPA) was HPLC grade; water was double-distilled and deionised. Microcrystalline cellulose (Avicel PH 301), vinylpyrrolidone-vinylacetate-copolymer (Kollidon VA 64), and magnesium stearate were of pharmaceutical grade. Salts used to create controlled humidity environments were laboratory reagent grade or better.

4.2. Methods

Ranitidine-HCl form I and form II powder samples were characterised before the stability study was initiated using X-ray powder diffraction (XRPD), hot stage microscopy (HSM), differential scanning calorimetry (DSC), elemental analysis and scanning electron microscopy (SEM).

4.2.1. X-ray powder diffraction (XRPD)

A wide-angle powder X-ray diffractometer composed of an X-ray diffraction generator (Philips PW 1130/00, Philips, Almelo, The Netherlands), equipped with a goniometer (Philips PW 1050, Philips, Almelo, The Netherlands) was used. A copper tube coupled with a graphite monochromator was used as the anode material (λ = 1.541 Å CuKα), and operated at 40 kV and 30 mA. The monochromator removed secondary fluorescence radiation from the samples, to improve the peak to background signal. The automatic divergence slit was 1° and the receiving slit was set at 0.1°. The takeoff angle was fixed at 3° 2Θ. The diffraction signals were recorded digitally at a scanning rate of 25 steps/°2Θ and a count time of 1 second/step from 3°–60° 2H scattering angle. They were then graphed and analysed by the software package MacDiff (free software by R. Petschick).

4.2.2. Hot stage microscopy (HSM)

A hot stage (Mettler FP82HT, Mettler-Toledo GmbH, Schwerzenbach, Switzerland) with central processor (Mettler FP90, Mettler-Toledo GmbH, CH-8603, Schwerzenbach, Switzerland), polarising light microscope (Nikon Optiphot, Nikon Corporation Instruments Division Tokyo, Japan) and photomonitor (ZU FP82, Mettler-Toledo GmbH, Schwerzenbach, Switzerland) was used to determine melting behaviour. Different heating rates (0.5 to 10 K/min) were used. Melting behaviour was determined by visual observation (100 × magnification) and by detection of transmission of light using the photomonitor.

4.2.3. Differential scanning calorimetry (DSC)

A DSC (Perkin Elmer Pyris 1, Norwalk, Connecticut, USA) was used. Purge gas was run at 10 ml/min and an air shield was also in place. The DSC was calibrated with indium (melting point: 156.6 °C) at a heating rate of 10 K/min. 2 mg of each powder sample was hermetically sealed in aluminum pans using a universal crimper (Perkin-Elmer, Norwalk, Connecticut, USA) and thermograms were recorded at the same heating rate as calibration (10 K/min) and analysed by a PC Perkin-Elmer software program.

4.2.4. Elemental analysis

C, H, N, S analyses were performed by gas chromatography using thermal conductivity with flash combustion (Carlo-Erba EA 1108, Elemental Service Lab, Chemistry Department, University of Otago).

4.2.5. Scanning electron microscopy (SEM)

Powder samples were subjected to sputter-coating under argon vacuum (Bio-Rad E5100, Bio-Rad Microscience Division, Watford, England) resulting in a thin gold/palladium layer (80 nm). A Cambridge S360 scanning electron microscope (Cambridge Instrument, Cambridge, England) which was operated with an acceleration voltage of 5 kV was used.

4.3. X-Ray powder diffraction determinations after pretreatment and storage

Samples that were in dry powdered form were placed into aluminium sample holders and compressed (by hand) by a flat surface puncher. Some moist samples (pastes) (recovered after storage but before drying) were treated in a similar way. Samples that were considerably liquefied were dried and powdered before analysis as above. Identification and quantitation of form I and form II content from the diffractograms were carried out. Peak height, area and base line of the characteristic peaks (°2Θ) of form II (F2(1): 20.02°, F2(2): 23.4°) and form I (F1(1): 17.04°, F1(2): 21.9°, F1(3): 24.8°) (Fig. 1), were used for quantitation via the regression and artificial neural network models developed earlier [6].

4.4. Sample pretreatment

4.4.1. Mixing of form I with form II or with excipients

Form I powder was mixed with form II in weight ratios of 50 : 50 and 99 : 1 and also mixed with the excipients (microcrystalline cellulose, vinylpyrrolidone-vinylacetate-copolymer, and magnesium stearate) in weight ratios of 56 : 44.

4.4.2. Compression

Form I powder (400 mg) was compressed under a mass of 5 tons or 15 tons (Hydraulic compressor RIK, Ring Press (00-25), Research & Industrial Instrument Company, London, England) using an IR die and punch (RIK D-01, Research & Industrial Instrument Company), with a diameter of 12.88 mm. After releasing pressure, the tablets laminated into several slices or pieces. For XRPD a portion of the laminated pieces was powdered; the remaining laminates were stored without grinding.

4.4.3. Solvent pretreatment

Powdered form I was pretreated with small amounts of three solvent systems (IPA, an IPA/water mixture [1 : 1 (v/v)], and water) in a weight ratio of 2.5 : 1. After mixing well, the solvent was removed. Samples pretreated with IPA were readily dried at room temperature, until their weight was constant. Powders to which water and the IPA/water mixture had been added were dried with rotary evaporation (Rotavapor R110, Watson Victor Ltd, Auckland, New Zealand) at 40 °C and further dried at 42 °C in a vacuum desiccator until the weight was constant. Freeze drying was also used for some batches of the water-pretreated samples. The liquefied sample was put into a −80 °C freezer for 4–6 h to form an off-white, frozen solid mass, which was then subjected to overnight vacuum drying. This procedure was repeated and continued until the mass was properly dry. The mass was then broken up, ground into powder, and sieved (400 µm). The obtained powder was frozen overnight, and then dried at 42 °C in a vacuum desiccator till the weight was constant. The dried samples were gently ground and sieved (400 µm) before XRPD investigation and storage.

4.5. Storage conditions

Each powdered sample (1.2–1.4 g and controls) was distributed after pretreatment into small glass vials (flat bottom; 14 mm diameter; 50 mm height). Samples (in triplicate) were exposed to different humidities (45% RH; 55% RH; 75% RH) by placing into plastic air tight containers (26 × 26 × 15 cm) containing appropriate saturated salt-solutions (45% RH: K_2CO_3; 55% RH: $Mg(NO_3)_2$ (at 20 °C), NH_4NO_3 (at 30 °C), NaBr (at 42 °C); 75% RH: NaCl) [9]. The containers were stored, protected from light, at different temperatures (20 °C, 30 °C, 42 °C). The various samples were stored at selected humidities and temperatures — a limited factorial design (Table). The samples were analysed regarding visual appearance, weight (moisture uptake) and by XRPD (identification and quantitation of the polymorphic form) at 1 week, 2 weeks, then monthly for up to 6 months. Controls of all samples were stored in sealed containers, protected from light, at the different temperatures and also at room temperature, without temperature control.

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