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Characterization of polymorphs and hydrates of GK-128, a serotonin$_3$ receptor antagonist

Shusei Ito [a,*], Mari Nishimura [a], Yumiko Kobayashi [a], Shigeru Itai [a],
Keiji Yamamoto [b]

[a] *Research Center, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshinocho, Ohmiya, Saitama 330, Japan*
[b] *Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoicho, Inageku, Chiba 263, Japan*

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Abstract

The polymorphic and pseudopolymorphic forms of GK-128, a newly developed benzothiochromenone derivative, were characterized by powder X-ray diffractometry, thermal analysis, infrared spectroscopy, near-infrared spectrometry and hot-stage microscopy. The intrinsic dissolution rates at various temperatures were measured using the static disk method. GK-128 was found to have at least two hydrates (hemihydrate and monohydrate) and two anhydrates (anhydrate I and anhydrate II). When each form was stored at 25°C with a range of 0 to 97% relative humidity (RH), anhydrate I and anhydrate II were transformed to hemihydrate and monohydrate at above 90% RH and above 70% RH, respectively, while the crystalline forms of hydrates did not change after storage for 4 weeks. Intrinsic dissolution tests indicated that monohydrate was the most stable of these forms, since its dissolution rate was the slowest and no crystal transformation was observed during the dissolution tests. On the basis of the intrinsic dissolution rate of each form and the solubility of monohydrate, the solubilities of other metastable forms were calculated in order to estimate the transition temperature and the heats of dissolution. The transition temperature of hemihydrate and monohydrate was found to be 47°C, and the heats of dissolution of anhydrate I and anhydrate II were 16.5 and 14.7 kJ/mol, respectively. © 1997 Elsevier Science B.V.

Keywords: GK-128; Hemihydrate; Monohydrate; Polymorphic form; Powder X-ray diffraction; Intrinsic dissolution rate; Transition temperature

1. Introduction

2-[(2-Methylimidazol-1-yl)methyl]benzo[*f*]-thio-chromen-1-one hydrochloride (GK-128, Fig. 1) is a newly developed serotonin$_3$ receptor

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[*] Corresponding author.

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antagonist (Ito et al., 1995). There are several useful reviews of the pharmaceutical applications of polymorphism and pseudopolymorphism (Haleblian and McCrone, 1969; Haleblian, 1975; Mewada et al., 1973; York, 1983), and the study of polymorphism and pseudopolymorphism of newly developed compounds is important. Therefore, investigations of polymorphism and pseudopolymorphism, e.g. identification of polymorphic forms, comparisons of the physicochemical properties of such forms, and changes in crystalline form, have been performed (Jozwiakowski et al., 1993; Uchida et al., 1993; Kitamura et al., 1994; Randall at al., 1995; Kitaoka et al., 1995a; Ikeda et al., 1995; Yamada et al., 1995; Carlton et al., 1996).

In the present study, the identification, solid state stability, and dissolution behavior of some GK-128 crystalline forms were examined by way of GK-128 preformulation study. Powder X-ray diffractometry, thermal analysis, infrared spectroscopy, and hot-stage microscopy are clearly useful for the study of polymorphism and pseudopolymorphism, and in this study near-infrared spectrometry (NIR), which was used by Drennen and Lodder (1990) for estimation of aspirin tablet quality, was performed as well, in order to obtain findings concerning water molecules. Kitaoka et al. (1995b) demonstrated that nafagrel hydrochloride had a hemihydrate and a monohydrate and that its hemihydrate was converted into monohydrate at above 75% RH. Therefore, for GK-128 crystalline samples obtained, changes in the crystalline forms in the presence of moisture were studied. A stability test at high temperature (65°C) was also performed to provide an early and rapid method for predicting stability. Drug efficiency might be affected by drug dissolution behavior, while it is difficult to determine with precision the solubility of metastable forms, since they may dissolve into the solvent accompanying a transformation to the stable phase. Two methods for the measurement of metastable form solubility have been proposed, as follows: first, solubility was determined by the dispersed amount method using excess amount sample (Shefter and Higuchi, 1963), and second, solubility was calculated based on the intrinsic dissolution rate of each form (Nogami et al., 1969). In the present study, the solubility of the metastable forms at 20, 25, 30, and 37°C were determined using the latter method. Furthermore, the transition temperature and the heats of dissolution of each form were estimated based on van't Hoff plots.

2. Materials and methods

2.1. Materials

GK-128 was synthesized by the synthetic department of Taisho Pharmaceutical (form A), and the purity of the compound used was above 99.9%. Different polymorphic forms were prepared by the recrystallization of form A from water at 5°C (form B) and by heating forms A and B at 170°C (form C) and 120°C (form D), respectively, for 1 h. All other chemicals and solvents used were of analytical reagent grade.

2.2. Identification of hydrates and anhydrates

2.2.1. Measurement of powder X-ray diffraction

The powder X-ray diffraction patterns were measured with an X-ray diffractometer (Model RAD-3C, Rigaku Denki). The conditions of measurement were as follows: target Cu, monochromator graphite, 40 kV, and current 30 mA.

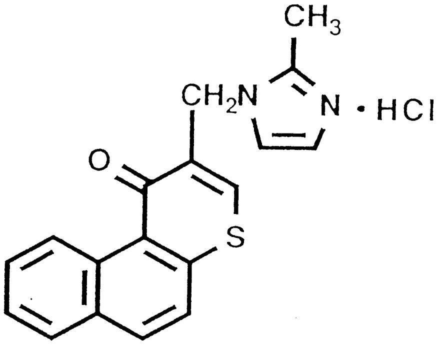

Fig. 1. Chemical structure of GK-128.

2.2.2. Thermal analysis

Differential scanning calorimetry (DSC) curves were determined with a differential scanning calorimeter (Model DSC7, Perkin-Elmer). Thermogravimetry (TG) curves were obtained with a thermogravimetric analyzer (Model TGA7, Perkin-Elmer). The DSC was operated under the following conditions: sample weight, about 3 mg; sample cell, an aluminum open cell with a cell cover; with heating rates varied in accordance with the purpose of the experiment. The conditions for TG were follows: sample weight, about 10 mg; sample cell, an aluminum open cell; with heating rates varied in accordance with the purpose of the experiment.

2.2.3. Infrared (IR) spectroscopy

IR spectra were measured by the KBr method using a Perkin-Elmer 1760 Fourier transform IR spectrophotometer.

2.2.4. Near-infrared (NIR) spectrometry

NIR spectra were measured using an Hitachi U-3500 spectrophotometer.

2.2.5. Water content determination

Water content was measured using a Karl Fischer titration apparatus (Model MKA-210, Kyoto Electronics).

2.2.6. Hot-stage microscopy

A Mettler FP-80 temperature programmer and a Mettler FP-82 hot-stage were used. Microscopic observations were made with a Nikon Optiphot2-pol polarized light microscope.

2.3. Stability studies

2.3.1. Moisture adsorption study

Accurately weighed amounts of each form were stored at various RHs. Conditions of 0, 9, 22, 31 and 97% RHs at 25°C were produced in a desiccator using silica gel or various saturated salt solutions, and 40, 50, 60, 70, 80, and 90% RHs at 25°C were produced using temperature and humidity chambers (Model SH-220, Tabai Espec). Weight changes were monitored after 7, 14 and 28 days and the phase changes were confirmed by X-ray diffractometry.

2.3.2. Stability at 65°C

Each form was stored in an oven (Model PH-3G, Tabai Espec) maintained at 65°C. Change in the crystalline form and chemical stability were confirmed by X-ray diffractometry and high performance liquid chromatography (HPLC), respectively. HPLC analysis was carried out using an Hitachi HPLC chromatograph composed of L-6000 and L-4000. The mobile phase (acetonitrile/pH 3 acetate buffer 2:3 (v/v) containing 0.5% (w/v) sodium lauryl sulfate) was delivered at a flow rate of 1.0 ml/min through a TSK-gel ODS 80TM column (4.0 mm I.D. × 15 cm; Tohso, Japan) at 50°C. The detection wavelength for GK-128 was 290 nm. Phenanthrene was used as an internal standard for HPLC.

2.4. Dissolution and solubility studies

2.4.1. Dissolution behaviors of crystalline powders

Excess amounts (about three times the concentration at saturation) of each sample were added to 100 ml of pH 4.0 acetate buffer solution ($\mu = 0.01$) maintained at 25°C, and immediately the mixture was shaken at 25°C using an incubator (Personal Lt-10 model, Taitec). The solution was sampled periodically with a pipette. After filtration (0.45 μm), the solution was appropriately diluted with the HPLC mobile phase solution. The concentration of GK-128 in the solution was measured by HPLC as described above.

2.4.2. Determination of solubility of monohydrate at different temperatures

The solubilities of form B, which is stable under our experimental conditions, were determined at 20, 25, 30 and 37°C by the dispersed amount method. Excess amounts (about three times the concentration at saturation) of sample were added to 10 ml of pH 4.0 acetate buffer solution maintained at 20, 25, 30 or 37°C, and the mixture was agitated vigorously at each temperature for 24 h using a shaker (Model SA31, Yamato Kagaku). After agitation, the solution was filtered (0.45 μm) and was appropriately diluted with acetate buffer. The above was carried out in a constant temperature room (Oriental Giken). The concentration of GK-128 was measured spectrophotometrically (Model LTV-160, Shimadzu Corporation) at 340 nm.

2.4.3. Measurement of intrinsic dissolution rate

The intrinsic dissolution rate of each form was measured by the static disk method using a Toyama Sangyo NTR-VS6P automatic dissolution apparatus. For disk preparation, a pressure of 300 kg/cm^2 was loaded for 3 min on 1 g of each form using a punch and die with 20 mm diameter. It was confirmed by powder X-ray diffraction that no polymorphic transition took place during the compression. The compressed disk was stuck on a thin columnar sinker of suitable size, such that only one surface of the disk contacted the liquid, and the remaining portion of the disk was covered with epoxide resin. The disk was set at the bottom of a dissolution flask with 500 ml of pH 4.0 acetate buffer solution maintained at 20, 25, 30 or 37°C. The dissolution medium was stirred at 50 rpm with a paddle positioned 3 cm from the bottom of the dissolution flask. At appropriate intervals, samples of solution were passed through a G-3 glass filter and delivered to the cell using the pump attached with the apparatus. The concentration of GK-128 was determined based on the absorbance at 340 nm. The sampling solution was returned to the original solution by the circulation system.

3. Results and discussion

3.1. Identification of hydrates and anhydrates

Powder X-ray diffraction patterns of forms A, B, C and D, which were respectively intact, prepared by recrystallization of form A from water at 5°C, prepared by heating form A at 170°C and by heating form B at 120°C are shown in Fig. 2. Significant differences in pattern were seen. Characteristic diffraction peaks were observed at $2\theta =$ 7.5, 15.1, and 22.7°C for form A, $2\theta = 5.7$, 12.4, and 16.7°C for form B, $2\theta = 7.4$, 12.6, and 22.3°C for form C, and $2\theta = 5.9$ and 12.0°C for form D, indicating that the crystalline structures differ from each other.

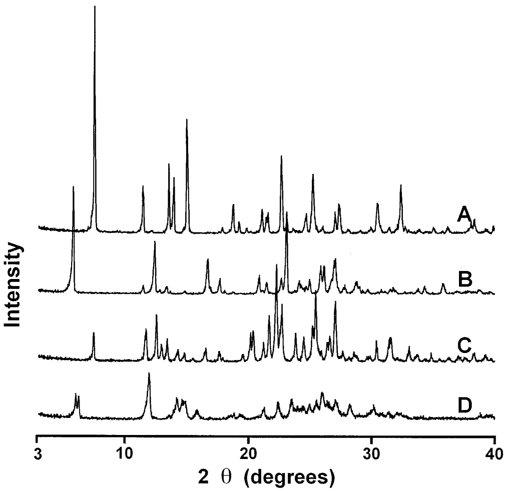

Fig. 2. Powder X-ray diffraction patterns of forms A, B, C and D.

On IR spectra (Fig. 3), each form exhibited unique spectral characteristics. Distinguishing IR absorption peaks for forms A and B were at 3426 and 3300 cm^{-1}, respectively, due to O–H stretching vibration of water molecules.

The DSC curves of forms A, B, C and D are depicted in Fig. 4, and the TG curves of forms A and B are reproduced in Fig. 5. In DSC measurements, forms A and B exhibited an endotherm due to dehydration at about 160 and 110°C, respectively, and in TG analyses, the weight losses corresponding to the endotherms of forms A and B were 2.5 and 5.0%, respectively. These weight losses, 2.5 and 5.0%, were nearly equal to the stoichiometric values calculated for the hemihydrate and monohydrate of GK-128, respectively, and were also identical with the percentages of water, 2.61 and 4.96% in forms A and B, respectively, measured by Karl Fischer titration. Furthermore, the activation energies for dehydration of forms A and B were estimated by the Ozawa method (Ozawa, 1965) based on TG data with change in the heating rate. The activation energy obtained for dehydration of form A, with ca. 2.5% water, was 128.1 kJ/mol and that of form B, with ca. 5.0% water, was 61.8 kJ/mol.

After dehydration, the DSC curves of forms A and were the same as those of forms C and D, respectively. Form A exhibited an endotherm at

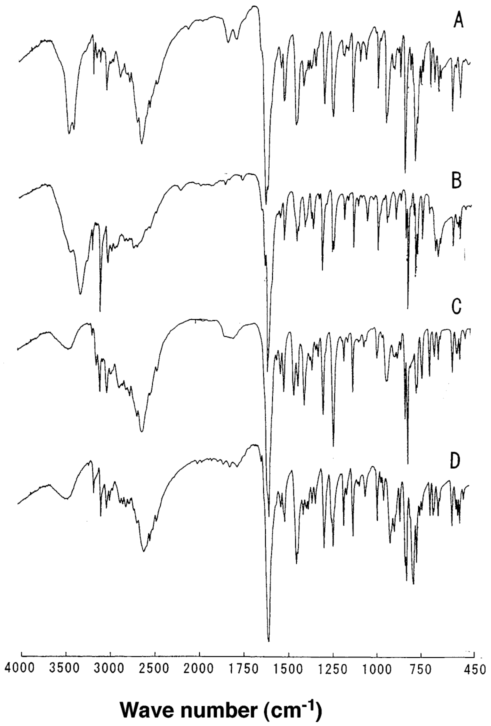

Fig. 3. IR spectra of forms A, B, C and D.

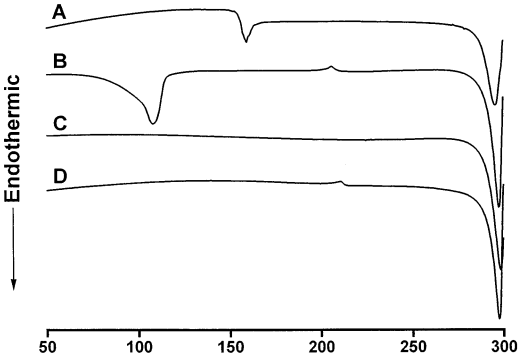

Fig. 4. DSC curves of forms B, C and D at a heating rate of 10°C/min.

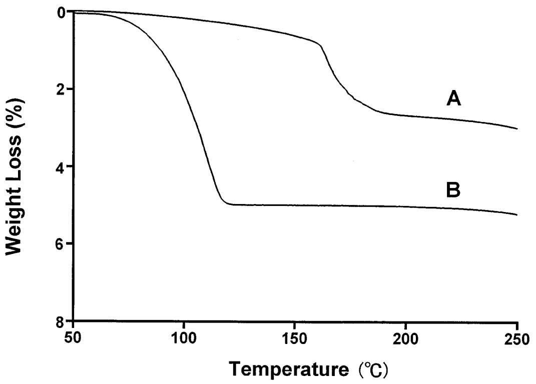

Fig. 5. TG curves of forms A and B at a heating rate of 10°C/min.

about 295°C due to melting of form C and form B exhibited an exotherm at about 210°C and an endotherm at about 295°C. The exotherm of the DSC curve for form D may have been due to a solid–solid transformation from form D to C, since the powder X-ray diffraction pattern of form D, heated at 250°C for 20 min, was the same as that of form C, and on hot-stage microscopic examination crystalline shape change were observed around 210°C. The heat of transition for form D → C, estimated from the exotherm on the DSC curve of form D, was − 0.80 kJ/mol. However, the heats of fusion for neither form C nor form D could be calculated from the thermograms, since the DSC curve for form D did not exhibit a sharp endotherm due to melting of form D as the heating rate was increased to 40°C/min in anticipation of the fusion prior to the transformation to form C, and the DSC curve for form C exhibited an endotherm at about 295°C, which subsequently underwent decomposition to reveal an exotherm at about 300°C.

The above results confirmed that the crystalline structures of forms A, B, C and D differ from each other, and that forms A and B are hydrates and forms C and D are anhydrates. Furthermore, forms A and B appear to be a hemihydrate and a monohydrate, respectively, and forms C and D are hereafter referred to as anhydrates I and II, respectively. It appears that anhydrates I and II might be monotropic, and that anhydrate I is usually more stable than anhydrate II, since the DSC curve of anhydrate II exhibited an exotherm attributed to the solid–solid transformation from anhydrate II to I (Burger and Ramberger, 1979).

NIR spectra of four samples are shown in Fig. 6. The peak patterns of the anhydrates, hemihydrate and monohydrate differed from each other, while those of the two anhydrates differed only minimally. Drennen and Lodder (1990) observed absorbance peaks of water molecules near 1450 and 1930 nm. In the case of GK-128, the peaks due to the crystalline water molecules of the hemihydrate and monohydrate were present at 1465 and 1980 nm, and at 1508 and 2028 nm, respectively. The water molecules in the hemihydrate crystal can be predicted to bond with GK-128 molecules more strongly than those in the monohydrate, since the NIR peaks attributed to the water molecules for the hemihydrate were observed at shorter wavelengths than those for the monohydrate. Above prediction is also supported by the finding of a difference between the activation energies for dehydration of the hemihydrate and monohydrate.

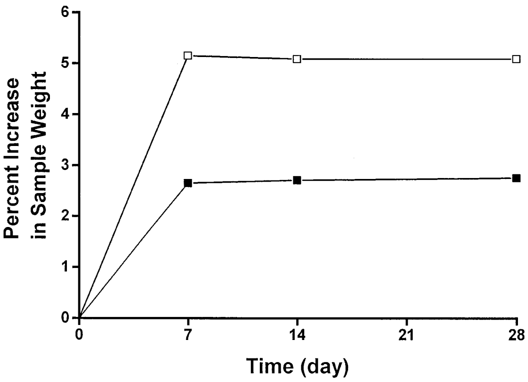

Fig. 7. Changes in water content of anhydrate I (■) and anhydrate II (□) during storage at 25°C and 97% RH.

3.2. Stability studies

Changes in water content of the anhydrates I and II during storage at 25°C and 97% RH are shown in Fig. 7. After storage for 7 days, water contents of anhydrates I and II reached about 2.5 and 5.0%, corresponding to the stoichiometric values calculated for the hemihydrate and monohydrate of GK-128, respectively, and no further significant changes were detected thereafter. The changes in crystalline forms of anhydrates I and II stored for 28 days were confirmed by powder X-ray diffractometry. The X-ray diffraction patterns of samples stored reveal that anhydrates I and II were transformed to the hemihydrate and monohydrate, respectively. Fig. 8 shows the water vapor adsorption isotherms of anhydrates I and II after storage at 25°C with various RHs. For anhydrate I, the considerable moisture adsorption occurred at above 90% RH, and conversion to the hemihydrate was confirmed by powder X-ray diffractometry. For anhydrate II, marked increase in weight occurred at above 70% RH, and changes in crystalline form to the monohydrate was observed by powder X-ray diffractometry. It can be predicted that if both the hemihydrate and monohydrate are present, the hemihydrate will usually be converted to the monohydrate at high RH. This occurrence was described for nafagrel hydrochloride by Kitaoka et al. (1995b). The hemihydrate of nafagrel hydrochloride was converted

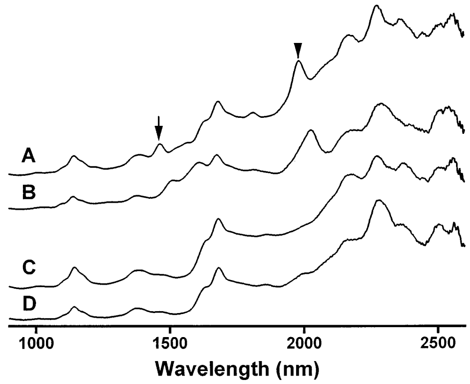

Fig. 6. NIR spectra of forms A, B, C and D. ↓: peak at 1465 nm, ▼: peak at 1980 nm.

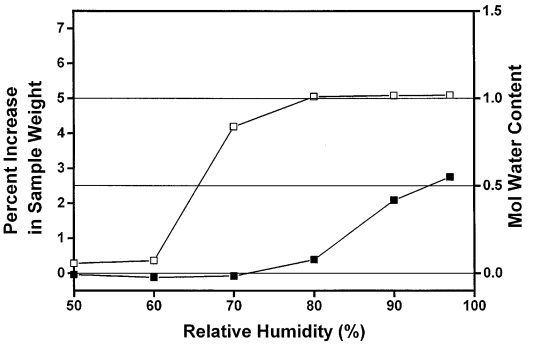

Fig. 8. Water vapor adsorption isotherms of anhydrate I (■) and anhydrate II (□) at 25°C.

to the monohydrate at above 75% RH. However, in the case of GK-128, after conversion from anhydrates I to the hemihydrate, no conversion from the hemihydrate to monohydrate took place. Furthermore, anhydrates I and II were converted to only the hemihydrate and monohydrate, respectively. Kitaoka et al. (1995a) reported that the difference in dehydration behavior between levofloxacin hemihydrate and monohydrate might be due to the difference in the crystalline structures of the hemihydrate and monohydrate. In the case of GK-128, the differences in physicochemical properties among anhydrates I and II, hemihydrate and monohydrate may also be clarified by considering the crystalline structure of each form. However, the crystalline structure of only the hemihydrate has been determined, since single-crystals of other forms have not yet been obtained.

On the other hand, no significant changes in sample weight or crystalline structure took place for the hemihydrate and monohydrate after storage between 0 to 97% for 28 days. As shown in Fig. 7, in the anhydrate I–hemihydrate system, anhydrate I was stable at less than 90% RH, while the hemihydrate was stable above 90% RH, and in the anhydrate II–monohydrate system, anhydrate II was stable at less than 70% RH, while the monohydrate was stable above 70% RH. Therefore, the finding that neither of the hydrates was converted to the anhydrate after storage at 0% RH for 28 days is contrary to the phase rule, according to which the hydrate and anhydrate cannot coexist in stable equilibrium over a range of vapor pressures at a constant temperature. Similar findings which are contrary to the phase rule have been reported for carbamazepine (Kaneniwa et al., 1984), calcium gluceptate (Suryanarayanan and Mitchell, 1986) and nafagrel hydrochloride (Kitaoka et al., 1995b), and in the studies of calcium gluceptate and nafagrel hydrochloride, interesting explanations for the opposition to the phase rule have been made. Suryanarayanan and Mitchell state as follows: calcium gluceptate has a hydrate containing 3.5 molecules of water per atom of calcium and a crystalline anhydrate, and both the hydrate and anhydrate are stable between 0 and 66% RH. The hydrate layer on the surface of the anhydrous crystals, which is formed initially by moisture adsorption, hinders the diffusion of water vapor, thus inhibiting the further conversion of the anhydrate to the hydrate. Kitaoka et al. demonstrated that nafagrel hydrochloride has a hemihydrate and monohydrate, and that both of the hydrates are stable between 23 and 64% RH. The kinetics and mechanism of dehydration of the hemihydrate and monohydrate differ and the monohydrate is dehydrated faster than the hemihydrate. The hemihydrate layer on the surface of the monohydrate crystals, which is formed initially by dehydration, hinders the elimination of crystalline water, thus inhibiting the further conversion of the monohydrate to the hemihydrate. The cause for the opposition to the phase rule may differ for each compound. In the case of GK-128, the observation that both the anhydrate and the hydrate were stable in the same RH range might be explained by the similar reason for the hydrate–anhydrate system of calcium gluceptate, and the finding that no conversion from the hemihydrate to the monohydrate took place might have been due to the similar cause for the hemihydrate–monohydrate system of nafagrel hydrochloride. However, the true nature of the phenomena concerning to the hydrate–anhydrate and hemihydrate–monohydrate systems of GK-128 remain unclear. When all the crystalline structures of GK-128 have been determined, further discussion of the relationship among the crystalline forms of GK-128 will be useful.

Wadke and Jacobson (1980) noted that stability studies under stress conditions are extremely useful for predicting stability under appropriate storage conditions. Solid-state stability studies of each form of GK-128 at 65°C were carried out. After storage for 7 days, neither chemical decomposition nor crystalline change was observed for either anhydrate. Since transformation from anhydrate II to anhydrate I, indicating conversion from a meta-stable form to a stable one, did not occur after storage at 65°C for 7 days, and on DSC measurement this transformation was observed at high temperature (210°C), it appears that change from anhydrate II to anhydrate I takes place to only a minimal extent at room tempera-

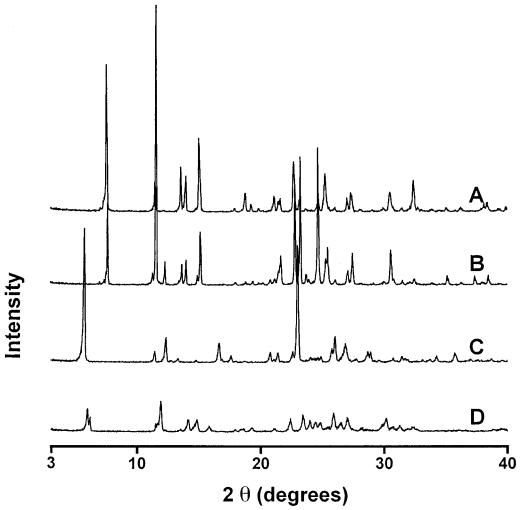

Fig. 9. Powder X-ray diffraction patterns of intact hemihydrate (A), hemihydrate stored at 65°C for 3 days (B), intact monohydrate (C) and monohydrate stored at 65°C for 3 days (D).

ture. The hemihydrate was chemically and physically stable after storage for 7 days, as were the anhydrates, while for the monohydrate the crystalline water was eliminated and, as shown in Fig. 9, the crystalline form was transformed to anhydrate II after storage for 3 days (no chemical decomposition was detected). The finding, that the monohydrate was dehydrated more easily than the hemihydrate at high temperature agrees with the findings of NIR and the activation energy for dehydration.

3.3. Dissolution and solubility studies

The dissolution patterns for different polymorphic and pseudopolymorphic forms in pH 4.0 acetate buffer solution at 25°C, determined by the dispersed amount method, are depicted in Fig. 10. For both anhydrates, the concentrations in bulk liquid increased rapidly, reaching maximum in an initial stage. The concentrations then fell gradually, with precipitation of the hydrates into the solid-phase. The maximum concentration of anhydrate II was higher than that of anhydrate I. After 2 h, the concentrations of anhydrates I and II fell to those of the hemihydrate and monohydrate, respectively, and no further concentration changes were observed after 24 h. The conversions from anhydrate I to hemihydrate and from anhydrate II to monohydrate agreed with the observations of the water vapor adsorption studies. On the other hand, for both hydrates, normal dissolution curves were obtained. In the case of the hemihydrate and monohydrate, concentrations of GK-128 reached constant values after ten min, and no further significant changes in concentration were detected after 24 h. The concentration of GK-128 after 24 h for the hemihydrate was 1.7 mg/ml higher than that for the monohydrate. These observations indicate that the monohydrate is most stable of the compounds tested under experimental conditions, and that the rates of transition from the anhydrates to hydrates in aqueous solution at 25°C may be rapid, while that from the hemihydrate to monohydrate might be extremely slow.

In the preformulation studies of the compounds having polymorphic and/or pseudopolymorphic forms, the estimates of thermodynamic differences between forms have often been made using individual solubility data (Behme et al., 1985; Ghodbane and McCauley, 1990; Chauvet et al., 1992). In the present study, solubilities of meta-stable forms were calculated using the method described by Nogami et al. (1969), based on dissolution rates. Disso-

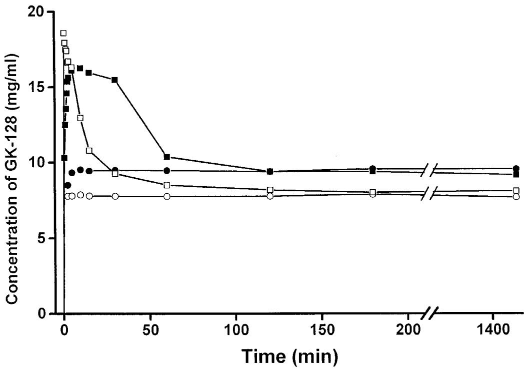

Fig. 10. Dissolution patterns for GK-128 from hemihydrate (●), monohydrate (○), anhydrate I (■) and II (□) in pH 4.0 acetate buffer solution at 25°C.

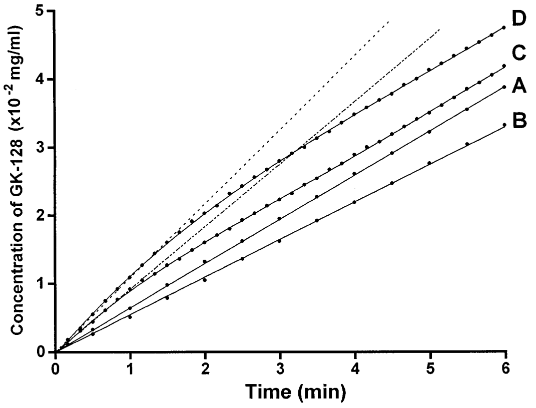

Fig. 11. Dissolution curves for GK-128 from hemihydrate (A), monohydrate (B), anhydrate I (C) and anhydrate II (D) in pH 4.0 acetate buffer solution at 25°C.

lution rates for the hydrates and anhydrates in pH 4.0 acetate buffer solution at 25°C were determined by the static disk method, and are illustrated in Fig. 11. The dissolution rates for both anhydrates were faster than those for the hydrates, and were decreased after 1–2 min, due to the phase transition. After examination, the changes in crystalline form on disk surfaces were confirmed. Anhydrates I and II were converted to the hemihydrate and monohydrate, respectively. On the other hand, the dissolution rates for the hemihydrate and monohydrate were constant during the entire run, and that of the hemihydrate was faster than that of the monohydrate. These observations agree with those obtained with the dispersed amount method, indicating that the monohydrate was the most stable of the compounds tested under experimental conditions. Since the dissolution patterns of GK-128 at 20, 30 and 37°C were similar to that at 25°C, the solubilities of the hemihydrate, anhydrate I and II at each temperature were calculated using the solubility of monohydrate and the dissolution rates of the individual forms. The solubility data for the hydrates and anhydrates are plotted in Fig. 12. The plots revealed a linear relationship between the logarithms of solubility and the reciprocal of absolute temperature. The heats of dissolution for the hemihydrate, monohydrate, and anhydrates I and II, calculated from the slopes in Fig. 11, were 26.7, 33.6, 16.5 and 14.7 kJ/mol, respectively. The transition temperature obtained from the intersection of the straight lines for the hemihydrate and monohydrate was 47.1°C. This temperature seemed reasonable given the finding that, when the hemihydrate crystal was dissolved in water at 80°C and the solution was cooled to 50°C, the hemihydrate crystal was obtained, and as the hemihydrate crystal was dissolved in water at 65°C and the solution was cooled to 20°C, the monohydrate crystal was obtained. The heat of transition from anhydrate II to anhydrate I, calculated from the difference in heats of dissolution, was −1.8 kJ/mol, and nearly equal to that estimated from thermal analysis (−0.80 kJ/mol).

4. Conclusions

Two hydrates (hemihydrate and monohydrate) and two anhydrates (anhydrate I and anhydrate II) were characterized by powder X-ray diffractometry, thermal analysis, infrared spectroscopy, near-infrared spectrometry, and hot-stage microscopy. Anhydrate I and anhydrate II were converted to the hemihydrate and monohydrate at 25°C and above 90% RH and 70% RH, respectively. However, no conversion of the hydrates was observed at 25°C over various ranges of RH. After storage for 3 days at

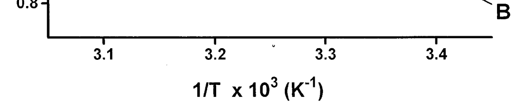

Fig. 12. van't Hoff for hemihydrate (A), monohydrate (B), anhydrate I (C) and anhydrate II (D) in pH 4.0 acetate buffer.

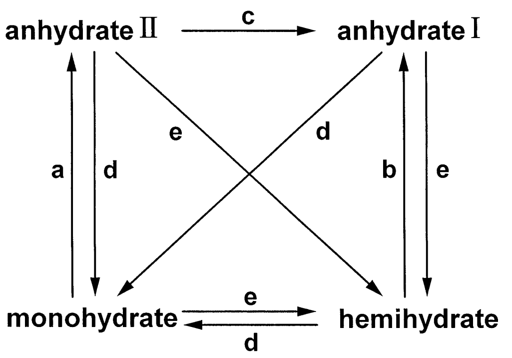

Fig. 13. Phase interconversion of GK-128. (a) Heating at 120°C, (b) heating at 170°C, (c) heating at 250°C, (d) crystallization in water at 5°C, (e) crystallization in water at 50°C.

65°C, the monohydrate had been transformed to anhydrate II by dehydration, while the crystalline form of hemihydrate was unchanged after storage for 7 days at the same temperature. On the other hand, in pH 4.0 acetate buffer solution, anhydrate I and anhydrate II were transformed rapidly to the hemihydrate and monohydrate at 25°C, respectively, and the transition temperature of the hemihydrate and monohydrate was about 47°C. Above this temperature, the hemihydrate was stable, while below this temperature the monohydrate was stable. The phase interconversion of GK-128 is illustrated in Fig. 13.

References

Behme, R.J., Brooke, D., Farney, R.F. and Kensler, T.T., Characterization of polymorphism of gepirone hydrochloride. *J Pharm. Sci.*, 74 (1985) 1041–1046.

Burger, A. and Ramberger, R., On the polymorphism of pharmaceuticals and other molecular crystals. I. *Mikrochim. Acta* [Wien], II (1979) 259–271.

Carlton, R.A., Difeo, T.J., Powner, T.H., Santos I. and Thompson, D., Preparation and characterization of polymorphs for an LTD4 antagonist, RG12525. *J. Pharm. Sci.*, 85 (1996) 461–467.

Chauvet, A., Masse, J., Ribet, J.P., Bigg, D. Autin, J.M., Maurel, J.L., Patoiseau, J.F. and J., Characterization of polymorphs and solvates of 3-amino-1-(*m*-trifluoromethylphenyl) - 6 - methyl - 1*H* - pyridazin - 4 - one. *J. Pharm. Sci.*, 81 (1992) 836–841.

Drennen, J.K. and Lodder, R.A., Nondestructive near-infrared analysis of intact tablets for determination of degradation products. *J. Pharm. Sci.*, 79 (1990) 622–627.

Ghodbane, S. and McCauley, J.A., Study of the polymorphism of 3-((3-(2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl) phenyl)((3-(dimethylamino-3-oxopropyl)thio) methyl)thio) propanoic acid (MK571) by DSC, TG, XRPD and solubility measurements. *Int. J. Pharm.*, 59 (1990) 281–286.

Haleblian, J. and McCrone, W., Pharmaceutical applications of polymorphism. *J. Pharm. Sci.*, 58 (1969) 911–929.

Haleblian, J.K., Characterization of habits and crystalline modification of solids and their pharmaceutical applications. *J. Pharm. Sci.*, 64 (1975) 1269–1288.

Ikeda, Y., Nishijima, K., Tokai, N. and Nishi, K., Kinetic studies of transition of seratrodast polymorphic forms by differential scanning calorimetry. *Yakugaku Zasshi*, 115 (1995) 937–943.

Ito, C., Isobe, Y., Kijima, H., Kiuchi, Y., Ohtsuki, H., Kawamura, R., Tsuchida, K. and Higuchi, S., The anti-emetic activity of GK-128 in *Suncus murinus*. *Eur. J. Pharmacol.*, 285 (1995) 37–43.

Jozwiakowski, M.J., Williams, S.O. and Hathaway, R.D., Relative physical stability of the solid forms of amiloride HCl. *Int. J. Pharm.*, 91 (1993) 195–207.

Kaneniwa, N., Yamaguchi, T., Watari, N. and Otsuka, M., Hygroscopicity of carbamazepine crystalline powders. *Yakugaku Zasshi*, 104 (1984) 184–190.

Kitamura, S., Chang, L. and Guillory, J.K., Polymorphism of mefloquine hydrochloride. *Int. J. Pharm.*, 101 (1994) 127–144.

Kitaoka, H., Wada, C., Moroi, R. and Hakusui, H., Effect of dehydration on the formation of levoflaxacin pseudopolymorphs. *Chem. Pharm. Bull.*, 43 (1995a) 649–653.

Kitaoka, H., Ohya, K. and Hakusui, H., Thermal dehydration of nafagrel hydrochloride hydrate at controlled water vapor partial pressures. *Chem. Pharm. Bull.*, 43 (1995b) 1744–1750.

Mewada, G.S., Parikh, D.R. and Somasekhara, S., Polymorphism in pharmaceuticals. *Sci. Cult.*, 39 (1973) 378–383.

Nogami, H., Nagai, T. and Yotsuyanagi, T., Dissolution phenomena of organic medicinals involving simultaneous phase changes. *Chem. Pharm. Bull.*, 17 (1969) 499–509.

Ozawa, T., A new method of analysing thermogravimetric data. *Bull. Chem. Soc. Jpn.*, 38 (1965) 1881–1886.

Randall, C.S., DiNenno, B.K., Schultz, R.K., Dayter, L., Konieczny, M. and Wunder, S.L., Solid-state transformation of a leukotriene antagonist. *Int. J. Pharm.*, 120 (1995) 235–245.

Shefter, E. and Higuchi, T., Dissolution behavior of crystalline solvate and nonsolvated forms of some pharmaceuticals. *J. Pharm. Sci.*, 52 (1963) 781–792.

Suryanarayanan, R. and Mitchell, A.G., Phase transitions of calcium gluceptate. *Int. J. Pharm.*, 32 (1986) 213–221.

Uchida, T., Yonemochi, E., Oguchi, T., Terada, K., Ya-