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Thermochimica Acta 288 (1996) 83–96

thermochimica acta

Assessment of the physical stability of lyophilized MK-0591 by differential scanning calorimetry

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Received 2 June 1996; accepted 14 June 1996

Abstract

MK-0591, a potent indirect leukotriene biosynthesis inhibitor, is poorly absorbed when administered orally as a crystalline sodium salt, primarily because of its low aqueous solubility (5 μg/mL). However, the lyophilized X-ray amorphous form with much higher aqueous solubility is very well absorbed and physically stable for long time periods. To better understand the physical stability of the amorphous state, conditions at which the compound will crystallize from the amorphous state were investigated in the context of its glass transition temperature. The physical stability of X-ray amorphous MK-0591 was evaluated by DSC with enhanced sensitivity using the crystallization exotherm at ca. 185°C (10°C/min) to detect crystallization in the solid matrix. No crystal formation was observed at 30°C for 6 months, 60°C for 6 months or 30°C at 75% RH for 6 months. This prolonged physical stability was attributable to two factors: its high glass transition temperature (ca. 125°C) and liquid crystal formation in aqueous solutions at concentrations greater than 60 mg/mL. Crystallization could not be induced after isothermally holding the X-ray amorphous MK-0591 at 120°C for 17 h. Seeding with crystalline MK-0591 (10%) also failed to induce crystallization at 50°C for 6 months or at 30°C at 75% RH for 6 months. Water plasticizes lyophilized MK-0591, lowering the T_g and inducing the onset of crystallization to 100°C. Crystallization at room temperature does not occur with equilibration at high relative humidites probably because of the additional stability imparted to the system by the formation of a lyotropic liquid crystalline phase. The behaviour of amorphous MK-0591, with its high T_g in the solid state and its liquid crystalline properties in concentrated aqueous solution, provided sufficient physical stability to permit its use in oral formulations.

Keywords: Determination of Crystallinity; Differential Scanning Calorimetry; L-686,708; Leukotriene Biosynthesis Inhibitor; Lyophilized; MK-0591; Oral Administration; Oral Formulations; Physical Stability; Thermal Analysis

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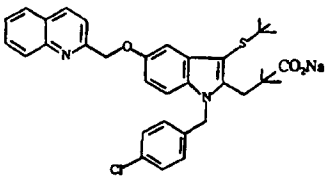
Elsevier Science B.V.
PII S0040-6031(96)03051-1

1. Introduction

Developing suitable solid formulations for oral administration of poorly water soluble drugs often can be very challenging. Characterizing the crystalline and amorphous solid-states of the drug substance is most important when optimizing drug absorption of these compounds.

Crystalline MK-0591, the sodium salt of 3-[1-[(4-chlorophenyl)methyl]-3-[9t-butylthio]-5-((2-quinoly)methoxy)-1H-indole-2]-α,α-dimethylpropanoic acid (see below), a potent indirect leukotriene biosynthesis inhibitor [1–3] melting at ca. 330°C, is physically and chemically very stable under conditions of thermal stress. However, as well-characterized, acicular crystals it is not well absorbed when orally administered to dogs primarily because of its low aqueous solubility (ca. 5 μg/mL).

The X-ray amorphous form, which is obtained either by lyophilization or by spray-drying, has an aqueous solubility of ca. 60 mg/mL [4], four orders of magnitude greater than that of the crystalline material. The resulting solution is supersaturated with respect to the crystalline solid state. In its amorphous form, MK-0591 is well absorbed. Because of the greater plasma levels obtained, X-ray amorphous MK-0591 was recommended for safety assessment studies to maximize animal systemic exposure without complicating the studies by the co-administration of solubilizing agents or nonaqueous solvents. Amorphous MK-0591 was evaluated as a potential solid state form of the drug for clinical formulations. However, using the amorphous, thermody namically metastable, MK-591 in a dosage form risks conversion to the more stable, poorly absorbed crystalline material. Evaluating and monitoring the physical stability of the amorphous material is critical to ensuring adequate drug delivery from the dosage form.



MK-0591

Preliminary observations indicated that X-ray amorphous MK-0591 did not crystallize after storage at or near ambient conditions. This study investigated temperatures and relative humidities which might induce crystallization using X-ray powder diffactometry, thermal analysis and water sorption techniques. Its primary intent was to better understand the nature of amorphous MK-0591 and define conditions under which it would crystallize or remain amorphous.

2. Experimental

2.1. Materials

The synthesis and characterization of MK-0591, a sodium salt, has been previously described [2]. The final crystalline form was obtained from ethanol. Lyophilization of

MK-0591 was carried out according to a process described elsewhere [5]. Crystalline MK-0591 is dissolved in hot water-ethanol solution, stripped of the alcohol content under vacuum, and tray lyophilized with secondary drying until the ethanol content is reduced to less than 0.5% (gas chromatography) and the water content to ca. 3% (Karl Fischer). Material obtained ranged in purity from 98.5% to 99.8% (HPLC).

2.2. Methods

2.2.1 X-Ray Powder Diffractometry

X-ray powder diffraction patterns were obtained on ground samples using a Philips X-ray powder diffractometer PW1840 with CuKα radiation (40kV x 30 mA). Alignment verification of the X-ray powder diffractometer was carried out with a silicon disk (silicon: 97.5% pure).

2.2.2. Differential Scanning Calorimetry (DSC)

A Seiko robotic DSC (RDC-220) was used to determine the glass transition temperature, T_g, and the enthalpy of crystallization of the lyophilized material. Crimped aluminum sample pans were used under a N_2 atmosphere (60 mL/min) at a scan rate of 10°C/min. Unless otherwise specified, the samples were dried by heating to 75°C at 20°C/min in open pans, and holding them isothermally at 75°C for 25 min. The samples were weighed and the pans crimped. The DSC was calibrated with gallium, indium and tin. Samples for T_g experiments were not dried unless the glass transition temperature of the dried sample was desired. The glass transition temperature experiments were carried out at 10 min and 40 °C/min and the T_g values were defined as the midpoints of the transitions.

2.2.3. Thermomicroscopy

Hot-stage polarized microscopy was employed from 30°C to 200°C using a Zeiss Universal Microscope with crossed polarizers and a Mettler FP-80 hot-stage at 10 °C/min.

2.2.4. Thermogravimetric Analysis (TGA)

Thermogravimetric analyses were carried out on a Seiko robotic TGA/DTA (RTG-220) at 10°C/min under N_2 (100 mL/min). The TGA was calibrated with indium and a standard 20 mg weight.

2.2.5. Thermomechanical Analysis (TMA)

TMA studies were carried out on a Seiko TMA120C by packing a TGA aluminum pan with the sample and placing a flat lid which floated on the sample. A 50 g load was used in compression with a compression/expansion quartz probe. The temperature scanning rate was 5°C/min or 40°C/min. The TMA was calibrated with indium.

2.2.6. Calibration Curve for the Measurement of Percent Crystallinity

In a previous study with MK-0591, small amounts of crystalline material were monitored by powder X-ray analysis using fixed ratios of crystalline and amorphous

material [6]. In the present study, DSC was used to evaluate crystallinity because of its convenience and improved sensitivity. Ground crystalline MK-0591 was added to samples of lyophilized MK-0591 in quantities ranging from 0% to 100%. The mixtures were shaken manually for 3 min. Samples of the blends (6 mg) were analyzed in triplicate by DSC.

Two assumptions were made. Firstly, X-ray amorphous material is 100% amorphous and crystalline MK-0591 is 100% crystalline. A standard curve was generated by measuring the crystallization enthalpies of Forms I and II (thermally obtained) of X-ray amorphous, lyophilized MK-0591 doped with crystalline MK-0591. Crystalline MK-0591 (which melts at 333°C with degradation) does not have transitions in the region of interest and does not contribute to the enthalpy of crystallization of lyophilized MK-0591. Enthalpies of crystallization were plotted against percent lyophilized material in the doped samples (Figure 1). A linear regression at the 95 % confidence interval was obtained with a slope of 0.296 ± 0.016, an intercept of 0.0093 ± 1.05 and a correlation coefficient of 0.998. From this calibration, a sample having a measured enthalpy of crystallization of -28.13 kJ/mol was estimated to be $95\% \pm 7\%$ amorphous.

The second exothermic transition due to the transformation of Form II to I also can be used to quantify the amount of crystalline MK-0591 (Fig. 2). A straight line of slope

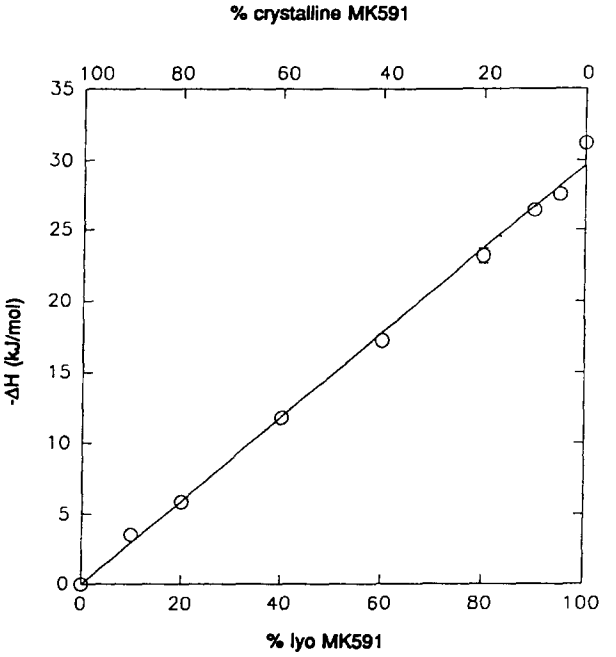


Fig. 1: Enthalpies of crystallization of the transition at 185°C (Form II). Standard deviations are smaller than the size of the circles.

0.0784 (with a 95% confidence range of 0.0684 to 0.0884) with an intercept of −0.32 (with a 95% confidence range of −0.979 to 0.342) and a correlation coefficient of 0.9899 was obtained. The second exothermic transition was only used as a means of verifying the results. The first calibration curve was used to monitor the physical stability of the lyophilized material.

2.2.7. Water Vapor Sorption

The moisture sorption/desorption isotherms of lyophilized MK-0591 were obtained at subambient pressures using a dynamic moisture balance, MB-300G with a CI microbalance (VTI Corporation, Hialeah, Florida). The moisture balance was calibrated with standard weights (1 mg to 100 mg). The moisture levels were verified using polyvinylpyrolidone and microcrystalline cellulose. Initially, samples were dried in vacuo at 60°C for 2h. This ensured no interference from residual solvent in the sample. Duplicate sorption/desorption isotherms at 30°C were obtained using sample weights of ca. 3 mg. The moisture levels were systematically varied from 0% RH to 90% RH and data obtained under equilibrium conditions. The criterion for achieving equilibrium was triplicate weights within ± 5 μg, taken at sampling intervals of 10 min.

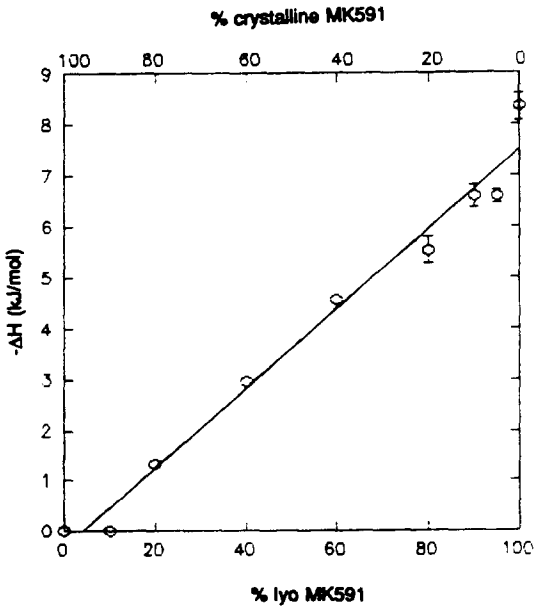


Fig. 2. Enthalpies of transformation of the transition at 254°C (Form II into Form I). Standard deviations are as shown or smaller than the size of the circles.

2.2.8. HPLC Analysis

HPLC analyses were performed on a Hewlett Packard 1050 series instrument (Palo Alto CA) equipped with a variable wavelength detector, a CSC Nucleosil-ODS (25 × 0.46) cm, 5 μm particle size column (Chromatography Sciences Co., Inc, St Laurent, Quebec). The mobile phase was an aqueous methanolic mixture modified with trifluoroacetic acid. The flow rate was 1.5 mL/min, the column temperature 50°C and detection wavelength 230 nm.

3. Results and discussion

3.1. Characterization of Crystalline MK-0591

Crystalline MK-0591 is a non-hygroscopic white free-flowing powder comprised of acicular particles. The X-ray diffraction pattern for crystalline MK-0591 is characteristic of a crystalline material (Fig. 3). The DSC scan is shown in Fig. 4. A melting endotherm concomitant with degradation (confirmed by HPLC analysis) was observed at an extrapolated onset temperature of ca. 333°C. Degradation onset was determined by TGA (Fig. 5) and occurred at temperatures greater than ca. 317°C on melting. No degradation was observed by TGA or HPLC analysis at temperatures

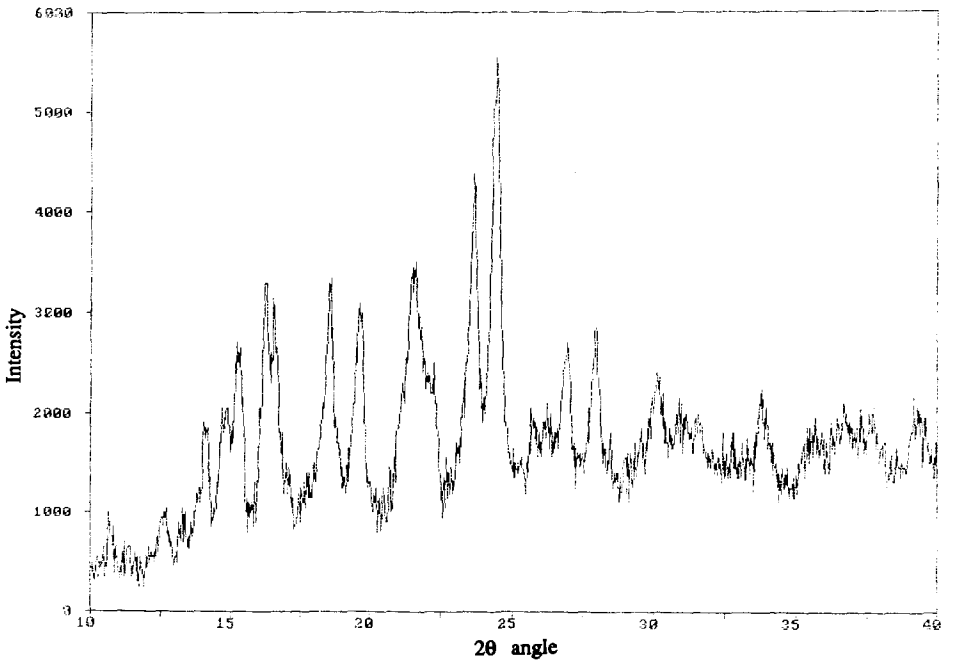


Fig. 3. X-ray powder diffraction pattern for crystalline MK-0591 (time constant = 0.2, receiving slit = 0.2, step width = 0.03, time = 1.5).

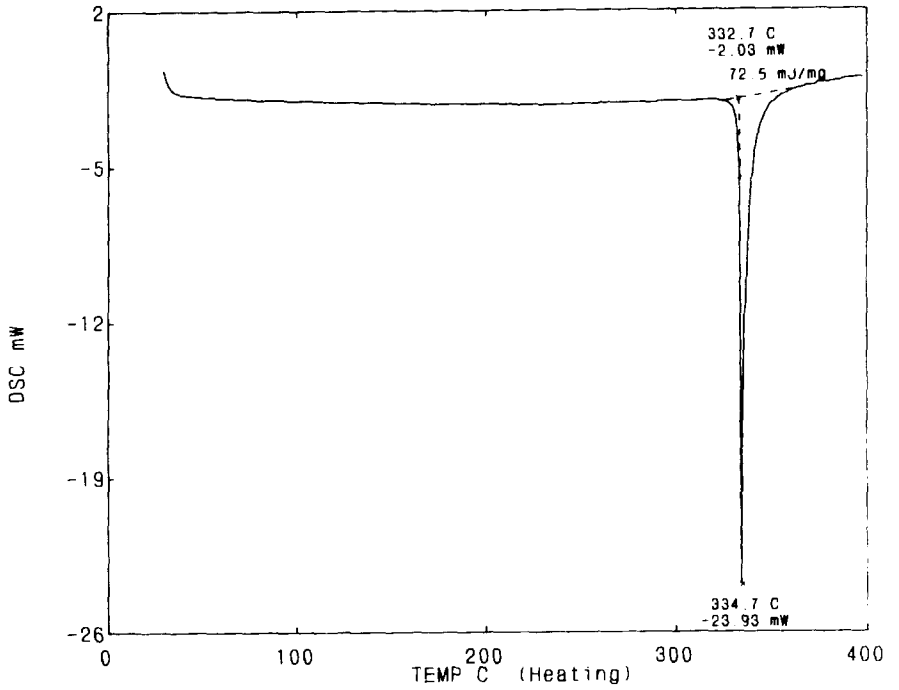


Fig. 4. DSC scan of crystalline MK-0591 (10°C/min). Endothermic transitions are down.

below the melt. No change in crystallinity was observed by powder X-ray diffractometry when crystalline MK-0591 was ground for 1 min–3 min by mortar and pestle. From the results reported earlier, detection levels of amorphous material in crystalline MK-0591 using X-ray powder techniques are about 5%–10% [6].

3.2. *Characterization of Lyophilized MK-0591*

The lyophilized material is amorphous by X-ray powder diffraction (Fig. 6). The DSC scan (10°C/min) of lyophilized MK-0591 (Fig. 7) showed 3 well-defined thermal events: 2 exotherms at extrapolated onset temperatures of ca. 181°C ($\Delta H = -3.3 \times 10^4$ J/mol) and 253°C ($\Delta H = 7.6 \times 10^3$ J/mol) and an endothermic event with an extrapolated onset temperature of ca. 324°C due to melting of the compound with degradation. A fourth event occurred at 120°C–130°C as a baseline deflection. This latter event was indicative of a glass transition and investigated further. The first exotherm (185°C) was assigned to crystallization from the amorphous matrix. Crystal formation was clearly observable by hot-stage microscopy. The second exotherm (253°C) was assigned to a solid-solid transition from the existing low temperature crystal form to another polymorphic crystal form. X-ray powder diffraction studies support this assignment and the two crystal forms, arbitarily, have been designated as

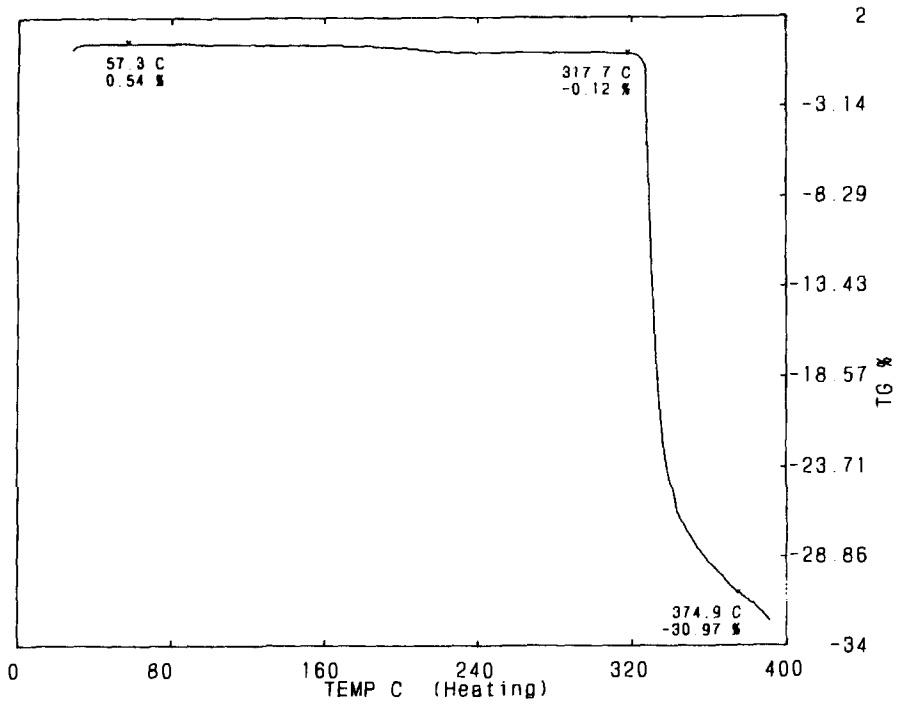


Fig. 5. TGA scan of crystalline MK-0591 (10°C/min).

Form II and Form I, respectively. The characteristics of Form I are identical with the crystal form obtained when MK-0591 is crystallized from ethanol. Quenching of the lyophilized material in the DSC, after having heated the sample through the the first exothermic peak (10°C/min) assigned to Form II crystallization, followed by rescanning at the same rate to 310°C, resulted in the appearance of only one exotherm at ca. 253°C (conversion of Form II to Form I). No thermal events were observed (from 40°C to 310°C) after quenching and heating a third time at the same rate, as would be expected if MK-0591 had existed as crystalline Form I prior to the third heating scan.

The observed glass transition temperature (T_g) determined by DSC at 40 °C/min was ca. 131°C. The T_g was observed at 125°C by TMA at 5 °C/min (Fig. 8). Since the T_g of a compound is the temperature at which there is an onset of molecular mobility on a experimental time scale of about 100 s, it is primarily a kinetically-controlled event [7]. Therefore, the T_g is sensitive to scan rates. Faster scan rates aid in observing the glass transition using DSC. The estimated value of the T_g at 10°C/min was 125°C. These determined T_g values were in agreement with the theoretically predicted value based on empirical values for polymeric materials where the T_g, generally is 2/3 of the melting temperature in K [8,9].

The solvent crystallized MK-0591 (Form I) has a higher temperature melting endotherm than crystalline MK-0591 formed by heating in the DSC (extrapolated

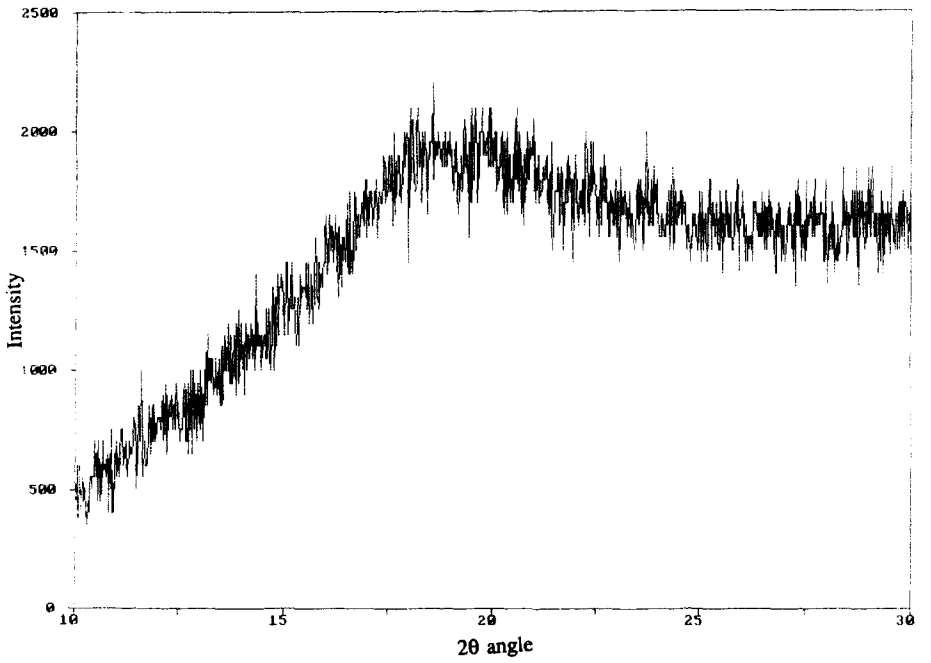


Fig. 6. X-ray powder diffraction pattern of lyophilized MK-0591 (time constant = 0.2, receiving slit = 0.2, step width = 0.03, time = 1.5).

onset temperatures: 333°C vs. 324°C). The temperature difference was attributed to differences in crystal habit. Acicular needles are formed when MK-0591 is crystallized from ethanol, while, an indefinite crystalline mass is formed from the melt. Grinding solvent-crystallized MK-0591 in a mortar and pestle reduces particle size and decreases the extrapolated melting onset temperature by 6°C. These differences cannot be explained by degradation (HPLC analysis) or by changes in the crystalline state as observed by X-ray powder diffractometry. Similar variations of phase transitions on particle size have been observed previously. For example, studies with phenethylamine bromide crystals of different sizes have donstrated that a temperature of onset for a solid-solid transition is dependent on particle size. Differences in onset temperatures of 10°C have been observed [10].

3.3. Crystallization from the lyophilized MK-0591

The straight line calibration curve obtained by adding crystallized MK-0591 to the lyophilized material and determining the area under the DSC peaks for the crystallization of Form II and the solid-solid transition of Form II to Form I, suggests that crystal growth and propagation from the lyophilized material do not occur during the DSC heating cycle as material is heated past the melt. There appears to be a large energy barrier to crystallization. Crystallization may be considered as a two-step process:

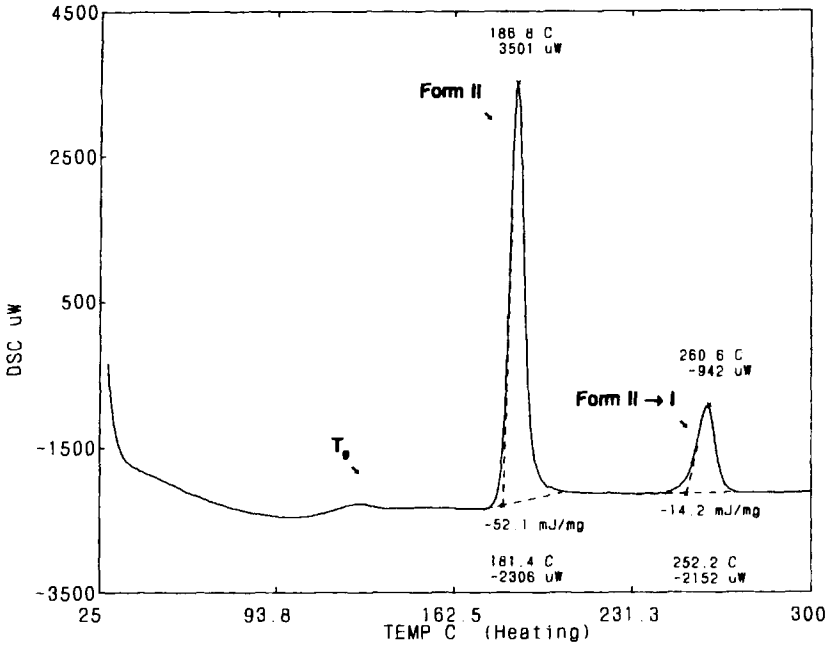


Fig. 7. DSC scan of lyophilized MK-0591 (10°C/min) (top) enlarged and (bottom) complete scan. Endothermic transitions are down.

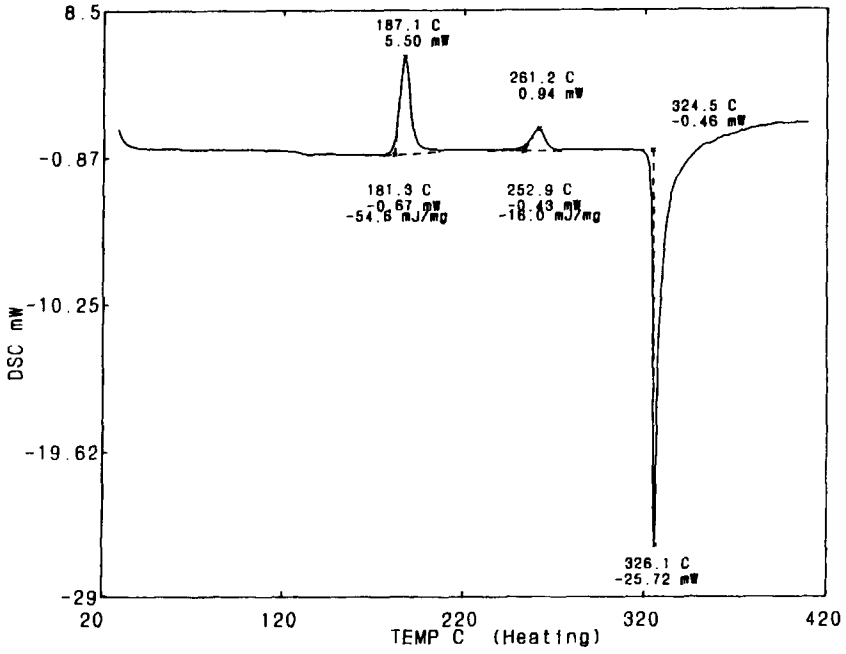


Fig. 7b.

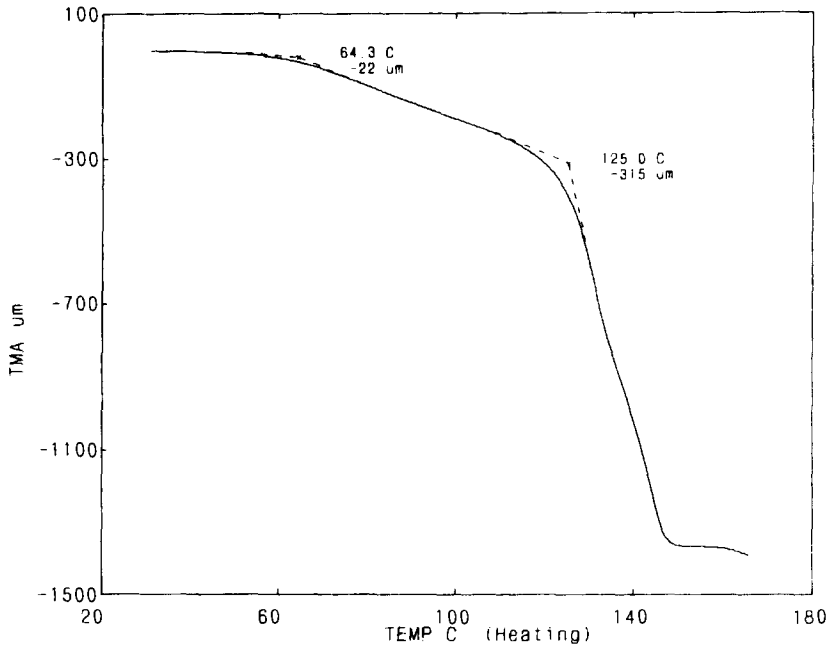


Fig. 8. TMA scan (5°C/min) with a 50 g load.

nucleation followed by propagation. Generally, nucleation is effectively induced by the addition of seed crystals of the compound. Crystalline MK-0591, ground with mortar and pestle and blended with X-ray amorphous MK-0591 should nucleate and accelerate the crystallization process in the DSC calibration experiments. However, crytallization did not occur. If the material were nucleated by the added crystallites (in essence a seeding process), the enthalpy of crystallization of the amorphous phase would be reduced (less material present to crystallize) and a concave upward curve would have been obtained. Seeding-induced crystallization has been demonstrated with sucrose and indomethacin [11,12]. Inhibition of crystallization in these studies must be due to the low molecular mobility at the temperatures studied.

Generally, dry materials with T_g values 50 K above room temperature have insufficient molecular mobility at room temperature to reorganize into crystalline material unless a plasticizer is present [7–9,11–14]. Since X-ray amorphous MK-0591 is 100°C below its Tg at ambient conditions, MK-0591 could remain amorphous at room temperature for extended periods of time. Experimental data indicated that crystallization could not be induced in dry, X-ray amorphous MK-0591 at 60°C for 6 months. Dry samples at 120°C overnight (17 h) did not crystallize. Samples seeded with ground crystalline MK-0591 (10%) did not crystallize at 50°C for 6 months and 30°C/75% RH for 6 months. Examples of similar behavior in the literature include X-ray amorphous β-acetyldigoxin and sulfathiazole (T_g = 62°C) which were reported as physically stable for prolonged time periods [15,16].

For pharmaceuticals, the most commonly occurring plasticizer is water [7,17,18]. If water plasticizes MK-0591, the T_g could be lowered such that crystallization could occur at room temperature. From the moisture sorption isotherms obtained (Fig. 9) it is apparent that lyophilized MK-0591 is hygroscopic, gaining approximately 25% by weight at 90% RH (30°C). Between 40% RH and 75% RH, the material becomes hard and granular. Between 75% RH and 90% RH, lyophilized MK-0591 becomes a clear hard fused material. Because of these observed morphological changes in the solid state with sorption of moisture, some hysteresis is observed on desorption from this fused material. However, samples stored at high humidity (30°C/75% RH) for extended time periods did not crystallize after 6 months even when seeded with crystalline MK-0591.

Attempts to measure the glass transition temperature of samples with different amounts of water failed because of the evaporation of the water during the DSC measurements. Sealed pans deformed because of the build-up of vapour pressure during the heating cycle. However, if a sample of X-ray amorphous MK-0591 stored at 30°C at 75% RH for one month was placed directly into the DSC at 100°C without permitting the sample sufficient time to dry, crystallization occurred at that temperature. A smaller than expected crystallization exotherm was observed at 185°C (Form II) and a second smaller exothermic solid-solid at exotic transition was observed at 254°C. These observations suggested that, in the presence of sorbed water, the more stable polymorphic Form I was obtained. A second sample of the same amorphous material equilibrated at 30°C at 75% RH was placed in the DSC at 30°C. No evidence for

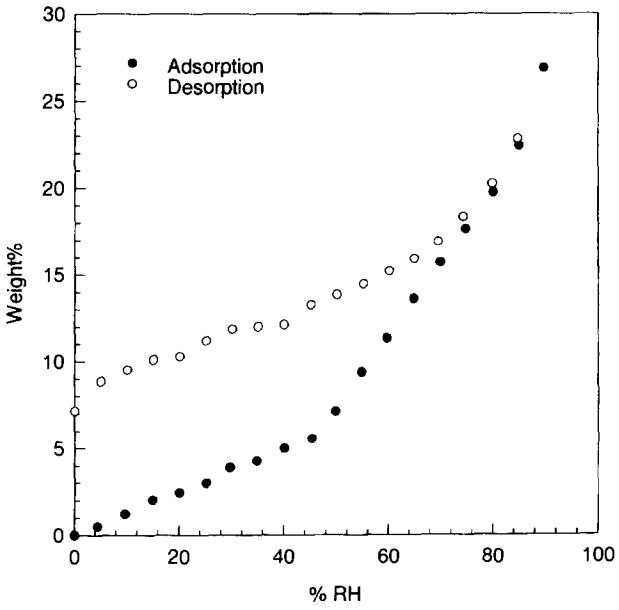


Fig. 9. Moisture sorption/desorption isotherm of lyophilized MK-0591 at 30°C after drying in vacuo for 2 h at 60°C.

crystallization was observed. The molecules, plasticized with sorbed moisture, had sufficient mobility at 100°C to organize into the crystalline form (but not at 30°C). The T_g had decreased from ca. 125°C for dry samples to approximately 100°C or lower for samples exposed to moisture (30°C at 75% RH).

Water has an additional effect on X-ray amorphous MK-0591. Increasing the water content leads to the formation of a lyotropic liquid crystalline phase. At concentrations greater than 60 mg/mL, birefringent patterns characteristic of the liquid crystalline state were observed by polarized light microscopy. Liquid crystalline materials have compositional but not positional order. They differ from crystalline materials which have both compositional and positional order. X-ray amorphous materials have neither positional nor compositional order [19]. Liquid crystalline materials generally are thermodynamically stable relative to the amorphous state but metastable relative to the crystalline state. MK-571, a leukotriene D_4 receptor antagonist with similar amphiphilic properties as MK-0591, organizes into both lyotropic and thermotropic liquid crystalline phases [20]. The ability of X-ray amorphous MK-0591 to form liquid crystalline solutions could impart additional stability with water sorption. This phenomenon may help to explain the observed stability of X-ray amorphous MK-0591 at 30°C at 75% RH.

4. Conclusions

Lyophilized MK-0591 is a hygroscopic, thermally stable, X-ray amorphous material. Its observed unique stability can be attributed primarily to its high glass transition temperature (ca. 125°C, mid-point, 10°C/min). A glass transition temperature ca. 100°C above ambient conditions implies limited molecular mobility at room temperature. Crystallization did not occur during storage at 60°C for 6 months. Studies with samples of X-ray amorphous MK-0591 seeded with ground crystalline MK-0591 (10%) failed to recrystallize during storage at 50°C for 6 months. No crystallization occurred at 120°C over 17 h in the absence of seed crystals. As has been demonstrated for indomethacin, sucrose, polyvinylpyrolidone and other polymers [11–14], there is insufficient molecular mobility at 50 K, or greater, below the glass transition temperature for the molecules to organize and crystallize into the thermodynamically more stable form.

Sorbed water plasticizes X-ray amorphous MK-0591 causing crystallization at 100°C. It lowers the glass transition temperature and induces crystallization by increasing molecular mobility. However, X-ray amorphous MK-0591 did not crystallize at 30°C at 75% RH during 6 months of storage when seeded with ground crystalline MK-0591 (10%). At concentrations greater than 60 mg/mL, X-ray amorphous MK-0591 forms a liquid crystalline phase in water. Generally, liquid crystalline materials are thermodynamically stable relative to the amorphous state and metastable relative to the crystalline state. The behaviour of amorphous MK-0591 with its high T_g in the solid state and its liquid crystalline properties in concentrated aqueous solutions provided sufficient physical stability to permit its use for oral formulations.

Acknowledgements

The authors wish to thank J.A. McCauley and R.J. Varsolona for their work in identifying Form II of MK-0591. B. Down is thanked for providing lyophilized samples of MK-0591. E. Kwong, M. Di Maso and S. McClintock, as well as L. Gravelle and J. Wybrandts are thanked for carrying out the HPLC work for bioavailability studies and stability assays.

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