Thermal Analysis and Solution Calorimetry Studies on Losartan Polymorphs

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INTRODUCTION

Losartan, an orally active nonpeptide-angiotensin II receptor antagonist, is a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl]-imidazole (Fig. 1). Losartan blocks the renin–angiotensin system by inhibiting the effects of angiotensin II directly at its receptors without the side effect of angiotensin converting enzyme inhibitors and exhibits a long half-life in the treatment of hypertension and congestive heart failure (1–3).

The thermal behavior of losartan was examined using differential scanning calorimetry. A remarkable endotherm at 276°C representing melting-decomposition was observed. However, a minor endotherm around 235–250°C was sometimes observed with some lots of material. This small endotherm is not related to impurity, hydrate, or solvate. It was demonstrated in the previous report that this crystalline form (Form I) was enantiotropically converted to another form (Form II) without melting, and the endotherm at 276°C was the melting-decomposition of Form II (4). These two polymorphic forms were confirmed using X-ray powder diffractometry. Form I is a thermodynamically stable polymorph at room temperature and is consistently obtained by solvent isolation. The current manufacturing process always generates only polymorphic Form I.

Since Form I converted to Form II prior to melting during the heating process, the heat of fusion cannot be determined by DSC. The heat of transformation measured by DSC did not reflect the true energy differences in the crystal lattice for these two polymorphs at room temperature.

Solution calorimetry has been used to investigate crystal properties, dissolution, complexation, stability, binding, and enzyme activity (5–7). Solution calorimetry can provide an accurate and satisfactory measurement of thermodynamic energy without temperature elevation. The shelf life of a drug solution at room temperature can be obtained in a shorter time frame and at realistic temperatures. In this study, solution calorimetry was used to confirm the losartan polymorphism and determine the thermodynamic differences between losartan polymorphs.

MATERIALS AND METHODS

Losartan, recrystallized from isopropanol/heptane (Form I) with a purity of >99%, was prepared at Chemical Process, Du Pont Merck, Chambers Works, Deepwater, NJ. A different crystalline form (Form II) was generated enantiotropically by heating Form I crystalline material in a 250°C oven for 10 min. The integrity of Form II was examined by a HPLC method.

X-ray powder diffractometry (XRPD) was used to identify the differences in crystal structures of these two forms. A Philips Model APD 3720 automated powder diffractometer equipped with a variable slit, a scintillation counter, and a graphite monochromator was used to examine losartan crystals. CuK_α radiation (40 kV, 30 mA) was employed. The sample was scanned from an angle (2θ) of 2 to 60°, with 0.02° increments. The intensity of the diffracted radiation was automatically detected every 0.5 sec by the scintillation detector.

The heat of solution was determined using a Tronac Model 450 calorimeter. About 100 to 150 mg of losartan was packed into a 1-mL glass ampoule, which was then sealed and placed in a holder equipped with hammer and stirring function. The device was then inserted into the reaction vessel containing solvent (water or *N,N*-dimethylformamide). The study was performed at 29°C. The glass ampoule was broken after the calibration baseline was established, and the heat of solution was recorded.

Differential scanning calorimetry (DSC) was conducted using TA Instrument DSC Model 910 equipped with Thermal Analyzer Model 1090. Losartan was placed in an hermetically sealed pan with the cover reversed and heated under a nitrogen stream from 30 to 300°C at a heating rate of 10°C/min. Thermal transitions were recorded.

Thermogravimetric analysis (TGA) was conducted using TA Instrument TGA Model 951 equipped with Thermal Analyzer Model 1090. The drug substance was heated under a nitrogen stream from 30 to 260°C at a heating rate of 10°C/min. The weight loss representing the volatile content was recorded.

HPLC analysis was used to determine the losartan concentration. The HPLC system included a Waters WISP 712 Autosampler, 510 HPLC pump, automated gradient control-

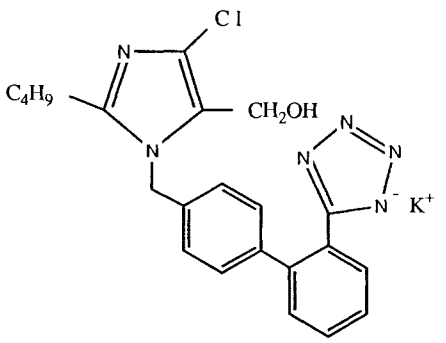

Fig. 1. The chemical structure of losartan.

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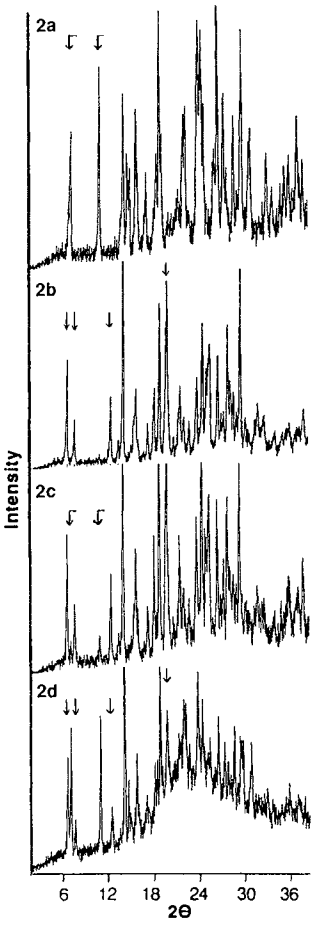

Fig. 2. X-ray powder diffraction patterns of losartan. Form I recrystallized from isopropanol/heptane mixture (a); Form II obtained by heating Form I in a 250°C oven for 10 min (b); some of the Form II converted to Form I after storage for 48 days (2). ⌜ indicates Form I identification peaks; more of Form II converted to Form I after storage for 1 year (2d). ↓ indicates Form II identification peaks.

ler with a flow rate setting of 1 mL/min, Nucleosil C-18, 25 cm × 4.6-mm-i.d column at 35°C, Applied Biosystem 757 Absorbance Detector with a wavelength setting of 254 nm, and HP LAS Lab Automatic recording and data analysis system. The mobile phase contained 35% aqueous acetonitrile, 0.1% (v/v) phosphoric acid, and the pH was adjusted to 3.0 with sodium hydroxide.

RESULTS AND DISCUSSION

The purities of losartan before (Form I) and after (Form II; heat-generated polymorph) heating were examined by HPLC, and no difference in purity was observed. This suggests that no degradation occurred during the heating process. X-ray powder diffraction patterns of Forms I and II are given in Figs. 2a and b. Three major regions at 2θ of 7–15, 19–21, and 23–26° are different for these two crystalline forms. XRPD is one of the most direct and widely used techniques to identify the morphology differences of crystalline powders, because different polymorphs have different molecular arrangement in the crystal lattice.

The heats of solution for polymorphs I and II, when dissolved in water and *N,N*-dimethylformamide, are summarized in Table I. The individual heats of solution are different for these two polymorphs. However, the differences for heat of transition using either water (ΔH_T is 1.723 kcal/mol) or *N,N*-dimethylformamide (ΔH_T is 1.757 kcal/mol) are insignificant. Since polymorphs are identical chemically and different in crystal structure, their heats of solution (ΔH_I and ΔH_{II}) are dependent on the solvents used. However, the heat of transition (ΔH_T) from Form I to Form II is independent of the solvent. The solution calorimetry results confirm that these two forms are polymorphs. The heats of solution of these two forms indicate that Form I is more endothermic than Form II. Therefore, Form I is more thermodynamically stable than Form II at ambient temperature.

Additionally, Form II gradually converted to Form I, since the conversion is exothermic (−1.74 kcal/mol). XRPD patterns of Form II 48 days and 1 year after storing under ambient conditions are given in Figs. 2c and d, respectively. It appears that Form II gradually and spontaneously converted to Form I. Form I identification peaks were observed in the Form II sample after 48 days of storage at room temperature (Fig. 2c). Most of the Form II crystals converted to Form I after 1 year of storage at room temperature as shown by XRPD (Fig. 2d).

A DSC thermogram of losartan is shown in Fig. 3. A minor endotherm around 230 to 250°C, followed by a remarkable endotherm at 276°C representing the melting-decomposition, was observed. Insignificant weight loss (0.2–0.3%) on thermogravimetric analysis from 30 to 265°C suggests that the small endotherm around 240°C was not solvent related. A lack of melting behavior for the temperature range 30 to 260°C using hot-stage microscopy suggests that the minor endotherm on DSC is not the melting of the material.

Table I. Heats of Solution of Losartan Polymorphs in Water and *N,N*-Dimethylformamide

Solvent	Heat of solution (kcal/mol)		Heat of transition, $\Delta H_T = \Delta H_I - \Delta H_{II}$
	ΔH_I	ΔH_{II}	
Water	2.288	0.665	1.623
	2.378	0.456	1.922
	2.275	0.650	1.625
Mean ± SD	2.313 ± 0.056	0.590 ± 0.117	1.723 ± 0.172
N,N-Dimethylformamide	−2.687	−4.458	1.771
	−2.501	−4.220	1.719
	−2.613	−4.393	1.780
Mean ± SD	−2.60 ± 0.094	−4.357 ± 0.123	1.757 ± 0.033

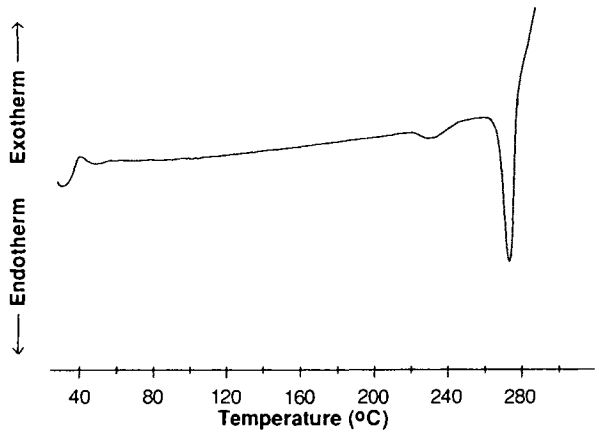

Fig. 3. Differential scanning calorimetric thermogram of losartan (Form I). Form I was transformed to Form II at 232°C and this Form II melted and decomposed at 276°C.

It was concluded that the minor endotherm corresponded to an enantiotropic polymorphic transition (4). However, the detectability of this small endotherm at 235°C varied from lot to lot and from run to run. The heat of transition determined by DSC ranged from 0 to 1.05 kcal/mol and was lower than that obtained by solution calorimetry. Since the material was heated on DSC before the polymorphic transition, the energy level of the heated sample is not the same as that of Form I at ambient temperature. Additionally, the specific sensitivity of DSC is not accurate enough to determine the heat flow at the microvolt/gram level. This probably resulted in the heat of transition varying from run to run and lot to lot. Since the enantiotropic transformation occurred before the melting of Form I, and Form II decomposed immediately after melting on DSC analysis, the heat of transition can not be computed from the heats of fusion. Solution calorimetry may be the only direct method to obtain an accurate heat of transition for a compound like losartan.

In conclusion, the existence of losartan polymorphs was confirmed by solution calorimetry. The heat of transition was determined to be 1.74 kcal/mol from Form I to Form II. Form I is thermodynamically more stable than Form II at ambient temperature. Form II could convert to Form I during storage at ambient temperature since the conversion is exothermic.

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