Physicochemical Characterization of Trazodone Hydrochloride Tetrahydrate

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Trazodone hydrochloride tetrahydrate was isolated and characterized by moisture absorption equilibrium, Karl Fischer method, powder X-ray diffractometry, infrared (IR) spectroscopy and elementary analysis. Trazodone hydrochloride (anhydrate) showed a supersaturation phenomenon in the dissolution process in water. In water and under high humidity condition (>93% relative humidity), trazodone hydrochloride was converted into the hydrate (trazodone hydrochloride : H_2O = 1 : 4). The hydrate dehydrated under less than 51% relative humidity at 25 °C. The activation energy for dehydration reaction from the hydrate to the anhydrate determined by a non-isothermal method (Ozawa method) was 37.1 kcal/mol.

Keywords trazodone hydrochloride; hydrate; dehydration; hygroscopicity; solubility; activation energy

Trazodone hydrochloride (2-[3-[4-(*m*-chlorophenyl)-1-piperazinyl]-propyl]-*s*-triazolo[4,3-*a*]pyridine-3(2*H*)-one monohydrochloride; TRZ) is a triazolopyridine derivative antidepressant. TRZ has overall therapeutic efficacy comparable with imipramine and amitriptyline in depressive illness. But, at dosages which have achieved a similar overall clinical improvement, TRZ causes fewer anticholinergic side effects than the tricyclic antidepressants.[1] We found that TRZ showed a supersaturation phenomenon in the dissolution process in water; this behavior suggests the presence of a hydrate of TRZ like other compounds.[2–4] The physicochemical properties of TRZ were reported,[5] but the hydrate of the substance has not been found. In this paper, we revealed the existence of TRZ hydrate and investigated its physicochemical characteristics. The difference in the physicochemical properties of crystal forms is an important factor affecting the stability and availability of pharmaceutical preparations. We report the hygroscopicity, the dissolution behaviors of the anhydrate and the hydrate of TRZ, and the thermodynamic property of dehydration of the hydrate.

Experimental

Materials TRZ anhydrate was supplied by A.C.R. Angelini Francesco (Rome, Italy).

Dissolution Experiments TRZ anhydrate (1 g) was introduced into distilled water (10 ml) maintained at 20 °C, and TRZ hydrate (0.4 g) was introduced into distilled water (5 ml) maintained at 20 °C. They were agitated by a magnetic stirring bar rotating at a constant speed. At suitable time intervals, the samples were withdrawn from the dissolution system and immediately filtered through a membrane filter (pore size 0.45 μm). The filtrate was diluted with an appropriate amount of distilled water, and analyzed spectrophotometrically at 312 nm using a Hitachi U-3000 spectrophotometer.

Moisture Absorption Equilibrium Samples were stored under 0, 11, 33, 51, 75, 84, 93 and 100% R.H. (relative humidity) at 25 °C. Each relative humidity condition was produced and maintained using diphosphorus pentaoxide or silica gel, the saturated aqueous solutions of lithium chloride, magnesium chloride, calcium nitrate, sodium chloride, potassium chloride and potassium nitrate, and distilled water, respectively. Samples stored under each relative humidity were weighed at suitable time intervals.

Loss on Drying TRZ hydrate (0.5 g) was heated at 105 °C until it reached a constant weight.

Karl Fischer Method A Kyoto Denshi Karl Fischer water content apparatus MK-AII was used.

Powder X-Ray Diffractometry A Rigaku Denki X-Ray diffraction analyzer with Ni-filtered Cu$K\alpha$ radiation was used.

IR Spectroscopy IR spectra were measured by the diffuse reflectance method using a Nicolet 60 SX Fourier transform IR spectrophotometer.

Elementary Analysis TRZ hydrate was analyzed by microorganic elementary analysis method using a Yanagimoto MT-3 CHN-corder.

Thermal Analysis Rigaku Denki TAS-100, TG–DTA 8112BS and DSC 8230B were used, and samples were placed on an aluminum pan. In thermogravimetry–differential thermal analysis (TG–DTA), the system was run at heating rates of 1, 2, 4 and 10 °C/min. In differential scanning calorimetry (DSC), the system was run at a heating rate of 10 °C/min using dry nitrogen (45 ml/min). The peak area was calibrated using indium as a standard sample.

Results and Discussion

Dissolution Behavior of TRZ Anhydrate Figure 1 shows the supersaturation phenomenon of TRZ anhydrate. It has been reported that for organic compounds having crystal water the solubility of the anhydrate is generally larger than that of the hydrate,[3,6,7] and a supersaturation phenomenon is caused by the formation of the hydrate.[2–4] Shefter and Higuchi stated that the maximum values observed in dissolution curves may correspond to the solubility of the anhydrous crystalline phase or represent a short-term steady-state phase situation involving equal rates of dissolution of the metastable form and crystallization of the stable hydrate.[3] We therefore concluded that TRZ hydrate existed.

Moisture Absorption Equilibrium of TRZ Anhydrate The hygroscopic behavior of TRZ anhydrate was investigated at various relative humidities at 25 °C. As shown in Fig. 2, above 93% R.H. it gradually absorbed water and even after 30 d did not reach an equilibrium state. We

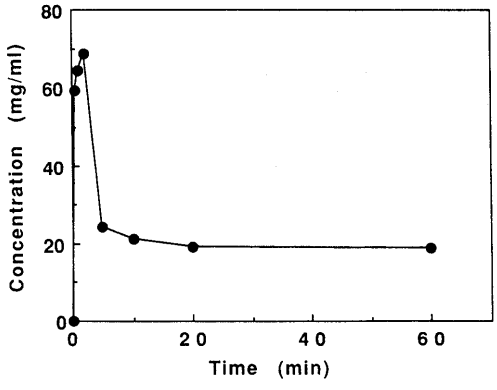

Fig. 1. Dissolution Behavior of TRZ Anhydrate in Distilled Water at 20 °C

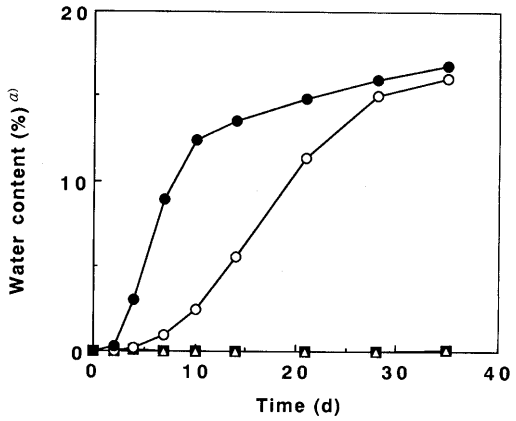

Fig. 2. Hygroscopic Behavior of TRZ Anhydrate at Various Relative Humidities at 25 °C

■, 75% R.H.; △, 84% R.H.; ○, 93% R.H.; ●, 100% R.H. *a*) Water content: weight of water/weight of anhydrate.

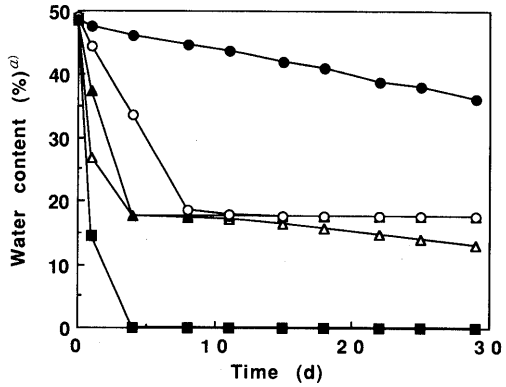

Fig. 3. Moisture Absorption Equilibrium of TRZ Anhydrate with Added Water (50%) at Various Relative Humidities at 25 °C

■, 0% R.H.; △, 51% R.H.; ▲, 75% R.H.; ○, 93% R.H.; ●, 100% R.H. *a*) Water content: weight of water/weight of anhydrate.

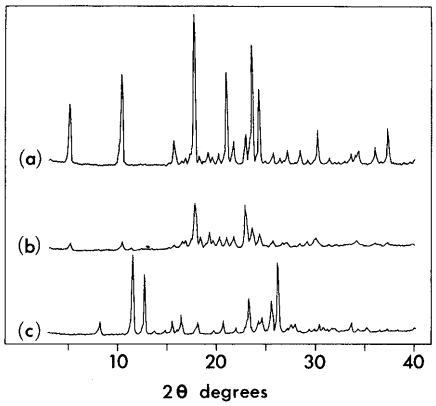

Fig. 4. Powder X-Ray Diffraction Patterns of TRZ Anhydrates and Hydrate

(a) TRZ anhydrate. (b) TRZ anhydrate obtained by dehydration of TRZ hydrate. (c) TRZ hydrate.

were unable to determine the number of water molecules in TRZ hydrate.

TRZ anhydrate with added water (50%) was stored at various relative humidities and weighed at suitable time intervals. As shown in Fig. 3, at 0% R.H. it immediately dehydrated to the anhydrate. At 51% R.H. the weight

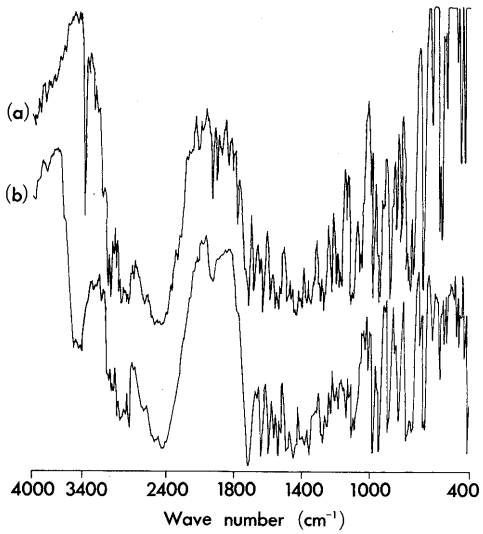

Fig. 5. IR Spectra of TRZ Anhydrate and Hydrate (Fourier Transform IR)

(a) TRZ anhydrate. (b) TRZ hydrate.

TABLE I. Elementary Analysis of TRZ Anhydrate and Hydrate

Form	Calcd (%)			Found (%)		
	C	H	N	C	H	N
Anhydrate	55.89	5.68	17.15	55.94	5.53	17.09
Hydrate	47.50[a)]	6.50[a)]	14.58[a)]	47.50	6.35	14.85

a) Assumed to be tetrahydrate.

change stopped when water content corresponded to tetrahydrate, then gradually began to dehydrate again. At 100% R.H. the adsorbed moisture was not easily desorbed. However, at 75 and 93% R.H. after the moisture was desorbed, it reached an equilibrium state when water content corresponded to tetrahydrate.

Identification of TRZ Hydrate On the basis of the above results, TRZ hydrate was prepared as follows: TRZ anhydrate dissolved in hot distilled water was left overnight at room temperature. TRZ hydrate recrystallized out was collected by filtration and stored at 75% R.H. at 25 °C until its weight became constant. Water content (weight of water/weight of anhydrate) of this sample was determined by loss on drying (17.4%) and Karl Fischer method (17.2%). This water content nearly corresponds to that of tetrahydrate (17.6%).

Figure 4 shows powder X-ray diffraction patterns of TRZ anhydrate, TRZ anhydrate obtained by dehydrating of TRZ hydrate and TRZ hydrate. The crystal form of TRZ hydrate was different from that of TRZ anhydrate. The anhydrate obtained by dehydrating has the same crystal form as the original anhydrate. Figure 5 shows IR spectra of TRZ anhydrate and TRZ hydrate. TRZ hydrate has a broad absorption band around 3450 cm^{-1} owing to the OH stretching vibration. Table I shows the result of elementary analysis of TRZ hydrate. Assuming that this hydrate is tetrahydrate, this value agrees very well with the theoretical value.

Characterization of TRZ Hydrate Figure 6 shows the dehydration behavior of TRZ hydrate at various relative

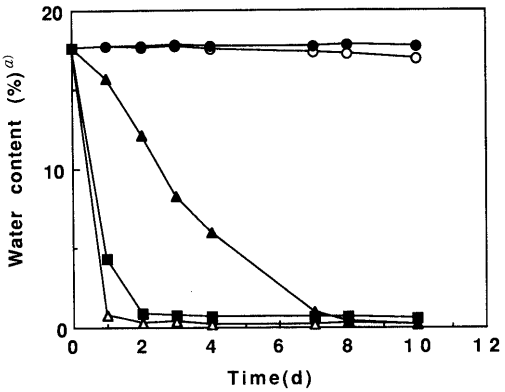

Fig. 6. Dehydration Behavior of TRZ Hydrate at Various Relative Humidities at 25 °C.

■, 0% R.H.; △, 11% R.H.; ▲, 33% R.H.; ○, 51% R.H.; ●, 75% R.H. *a*) Water content: weight of water/weight of anhydrate.

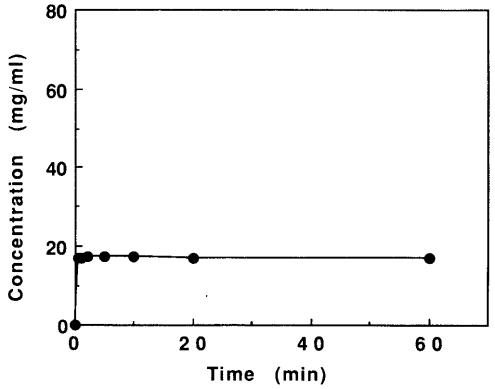

Fig. 7. Dissolution Behavior of TRZ Hydrate in Distilled Water at 20 °C

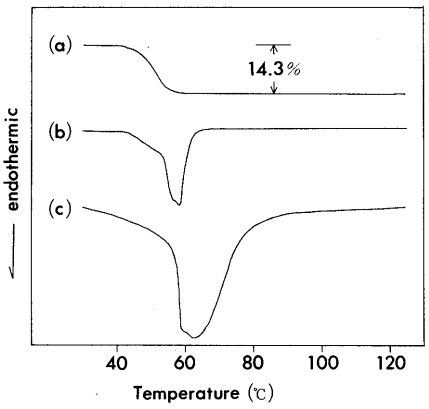

Fig. 8. TG, DTA and DSC Curves of TRZ Hydrate

(a) TG curve (heating rate: 2 °C/min). (b) DTA curve (heating rate: 2 °C/min). (c) DSC curve (heating rate: 10 °C/min).

humidities at 25 °C. At 0 and 11% R.H. it dehydrated rapidly, and at 51% R.H. just gradually, while at 75% R.H. it did not dehydrate at all. These results suggest that at below 51% R.H. dehydration of TRZ hydrate occurs easily.

Figure 7 shows the dissolution behavior of TRZ hydrate. TRZ anhydrate dissolved rapidly showing a supersaturation phenomenon (Fig. 1). TRZ hydrate, however, did not show such a phenomenon, and the solubility of hydrate corresponded to that of TRZ anhydrate at an equilibrium

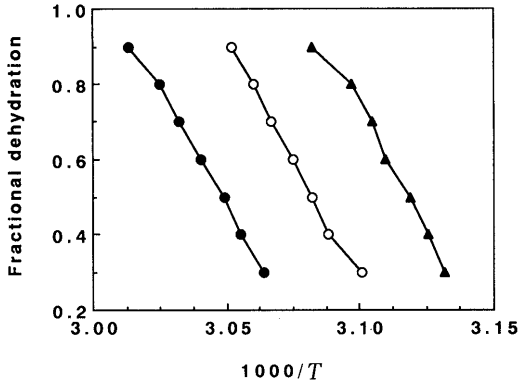

Fig. 9. Plots of Fractional Dehydration of the Hydrate *versus* Reciprocal of Absolute Temperature

Heating rate: ▲, 1 °C/min; ○, 2 °C/min; ●, 4 °C/min.

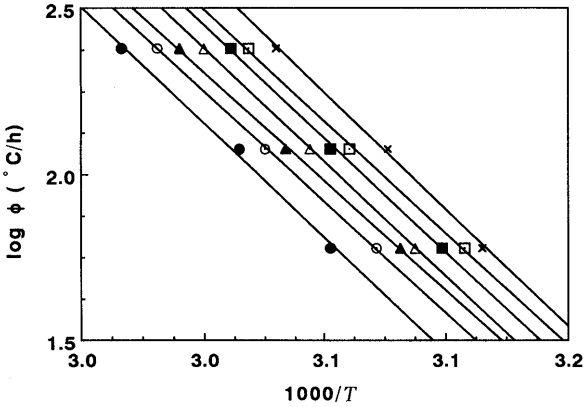

Fig. 10. Plots of Logarithms of Heating Rate *versus* Reciprocal of Absolute Temperature for Indicated Fractional Dehydration of the Hydrate

Fractional dehydration: ×, 0.3; □, 0.4; ■, 0.5; △, 0.6; ▲, 0.7; ○, 0.8; ●, 0.9.

state after the supersaturation. From the results of Figs. 1 and 7, it is considered that the metastable TRZ anhydrate transformed to the stable hydrate in the dissolution experiment of the anhydrate.

Figure 8 shows the results of thermal analysis of TRZ hydrate; dehydration began at about 40 °C. The heat of dehydration measured by DSC was 91.3 kcal/mol. The activation energy of the dehydration was determined by the method reported by Ozawa using TG.[8] As shown in Fig. 9, the plots of fractional dehydration of the hydrate (α) *versus* reciprocal of absolute temperature ($1/T$) have similar patterns regardless of the heating rate. This suggests that the dehydration process may consist of the same simple reaction mode.[8] As shown in Fig. 10, the logarithms of the heating rate ($\log \phi$) were plotted against reciprocal of absolute temperature ($1/T$) for indicated fractional dehydration. Straight lines were drawn by the method of least squares; the average of the activation energies determined from these lines was 37.1 kcal/mol. The activation energy of dehydration was a similar value to those of the other drugs.[2,9-13]

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