International Journal of Pharmaceutics, 74 (1991) 77–82
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ADONIS 037851739100277L

IJP 02461

Note

Solid state studies on Stiripentol: a novel anticonvulsant drug

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(Received 22 November 1990)
(Modified version received 4 March 1991)
(Accepted 11 March 1991)

Key words: Stiripentol; Antiepileptic; Racemate compound; Glass transition; Solid state; X-ray powder diffraction; Differential scanning calorimetry; Infrared spectrometry

Summary

Stiripentol, which exhibits antiepileptic properties is the E(±) 4,4-dimethyl-1-(3,4-methylenedioxyphenyl)-1-penten-3-ol. Solid state data obtained by means of X-ray powder diffractometry, differential scanning calorimetry, infrared spectrometry and solubility studies are given for quality control of the raw material. Stiripentol is an example of a racemate compound that easily forms persistent glasses whose thermodynamic properties are described and compared to those of the corresponding crystalline material.

Nowadays, solid-state criteria for unambiguous knowledge and identification of new drugs are required since it is well established that they may be concerned with polymorphism which may affect bioavailability, pharmacological properties and toxicity.

The present study has been undertaken in order to control the identity and the quality of several preindustrial batches of Stiripentol, and to ensure that no polymorphism appears at the end of their preparation.

Stiripentol (STP) [$C_{14}H_{18}O_3$, M = 234.3, E(±) 4,4-dimethyl-1-(3,4-methylenedioxyphenyl)-1-penten-3-ol] is a novel drug with antiepileptic properties (Lin et al., 1984; Vincent, 1986) that is not related to existing drugs, as quoted by Lisgarten and Palmer (1988).

Since one asymmetric C-atom and one ethylenic bond are present in the molecule, four isomers [Z(+), Z(−), E(+), E(−)] and two racemates (Z(±), E(±)) are expected to exist.

This work is a continuation of the previous crystal structure determination of the E(±) racemate (Lisgarten and Palmer, 1988; Toffoli et al.,

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TABLE 1

X-ray powder diffraction data of micronized Stiripentol

hkl	I_{obs} [a]	d_{obs}(Å) [a]	d_{cal}(Å) [b]	θ_{cal}(°)	θ_{obs}(°) [c]	$(I/I_M)_{obs}$ [c]	$(I/I_M)_{cal}$ [a]
100	m	14.07	14.03	3.15	3.16	20	98
$\bar{1}02$	m	7.28	7.265	6.09	6.09	19	23
002	vw	6.53	6.509	6.80	–	–	2
110	mw	5.613	5.610	7.89	8.01	43	8
011	s	5.534	5.539	7.99			42
$\bar{1}11$			5.521	8.02			19
102	m	5.107	5.103	8.68	8.70	19	13
$\bar{3}02$	s	4.993	4.994	8.87	8.88	48	47
111	w	4.857	4.848	9.14	–	–	4
$\bar{2}11$	w	4.805	4.813	9.21	–	–	4
$\bar{1}12$	vs	4.691	4.681	9.47	9.48	100	100
210	s	4.619	4.612	9.61	9.61	46	56
$\bar{2}12$	w	4.425	4.422	10.03	–	–	1
202	vw	3.983	3.972	11.18	11.19	6	3
112	w	3.922	3.919	11.33	11.35	11	13
$\bar{1}13$	w	3.774	3.772	11.78	11.86	26	18
$\bar{2}13$	mw	3.759	3.755	11.84			14
310	w	3.720	3.717	11.96	–	–	6
$\bar{2}04$	s	3.638	3.632	12.24	12.25	50	45
013	m	3.545	3.540	12.57	12.59	36	20
$\bar{1}04$			3.535	12.58			7
400	w	3.504	3.509	12.68	12.72	10	3
$\bar{3}04$			3.498	12.72			7
212	mw	3.336	3.332	13.37	13.38	13	8
$\bar{4}12$	vw	3.287	3.286	13.56	–	–	< 1
311			3.281	13.58	–	–	1
$\bar{4}11$	vw	3.258	3.255	13.69	–	–	1
004			3.255	13.69	–	–	1
$\bar{2}14$	ms	3.129	3.124	14.28	14.29	26	14
$\bar{4}13$			3.121	14.29			5
$\bar{1}14$	ms	3.066	3.061	14.57	14.58	28	20
020			3.060	14.58			5
120	w	2.996	2.990	14.93	14.98	4	4
021	w	2.981	2.979	14.99			2
$\bar{1}21$			2.976	15.00			1
104	w	2.905	2.900	15.41	15.42	7	5
$\bar{2}21$	w	2.851	2.848	15.69	15.73	7	7
312	w	2.829	2.826	15.81	15.84	7	2
$\bar{1}22$			2.820	15.85			3

TABLE 1 (continued)

hkl	I_{obs} [a]	d_{obs}(Å) [a]	d_{cal}(Å) [b]	θ_{cal}(°)	θ_{obs}(°) [c]	$(I/I_M)_{obs}$ [c]	$(I/I_M)_{cal}$ [a]
$\bar{2}15$	ms	2.623	2.618	17.11	17.14	11	7
$\bar{3}22$	w	2.614	2.609	17.17			1
$\bar{3}15$			2.609	17.17			1
$\bar{1}23$	vw	2.580	2.579	17.38	–	–	1
320	vw	2.565	2.561	17.50	17.51	3	3
510	vw	2.558	2.551	17.57	17.61	7	2
204			2.551	17.57			1
$\bar{1}15$	vw	2.544	2.540	17.65			3
222	w	2.424	2.424	18.53	18.56	3	2
$\bar{3}06$			2.422	18.55			1
015	w	2.399	2.396	18.75	–	–	1
$\bar{4}21$			2.394	18.77	–	–	< 1
$\bar{6}12$			2.393	18.78	–	–	< 1
$\bar{5}15$	w	2.357	2.360	19.05	–	–	< 1
214			2.355	19.09	–	–	2
$\bar{2}24$	w	2.345	2.340	19.22	–	–	1
$\bar{4}23$			2.339	19.22	–	–	< 1
600			2.339	19.23	–	–	< 1
$\bar{3}16$	w	2.255	2.252	20.00	–	–	2
$\bar{7}02$	w	2.215	2.213	20.37	20.39	9	4
$\bar{4}24$			2.211	20.39			1
322			2.207	20.43			1
$\bar{5}22$	w	2.189	2.189	20.60	–	–	< 1
610			2.185	20.64	–	–	2
006	w	2.177	2.170	20.79	20.84	4	3
$\bar{5}23$	w	2.164	2.163	20.87			2

[a] I_{obs} and d_{obs} from Guinier film (Enraf-Nonius FR 552 camera, $\lambda CuK\alpha_1 = 1.5405$ Å, 50 kV, 20 mA); visually estimated intensities: v = very, s = strong, m = medium, w = weak.

[b] Interplanar distances d_{cal} and calculated relative intensities $(I/I_M)_{cal}$ obtained with the data from Toffoli et al. (1988).

[c] θ_{obs} and $(I/I_M)_{obs}$ from automated diffractometer spectrum (Philips PC-APD PW 1877 system, $\lambda CuK\alpha_1$, 40 kV, 15 mA).

1988), which is monoclinic, $P2_1/c$, $a = 15.667$ Å, $b = 6.120$ Å, $c = 14.533$ Å, $\beta = 116.39°$, $Z = 4$.

Using the data from Toffoli et al. (1988), the interplanar distances d_{cal} (Å) versus *hkl* indices have been calculated for indexing the d_{obs} spacings obtained by means of a Guinier camera from crystalline powdered samples. Results collected in Table 1 show very good agreement between d_{obs} and d_{cal} values. Since no unindexed d_{obs} spacing is observed, one can assume that the samples correspond to the crystal structure. However, the intensities of the diffraction lines are estimated visually. In order to obtain intensity values, $I = f(\theta)$ scans were performed. Results are given in Table 1. The obtained θ-values agree with the calculated ones.

X-ray diffraction data, as recommended by the Joint Committee on Powder Diffraction Standards, based upon crystal structure determinations, may be used for the identification of crystalline materials. As shown in this paper, the Guinier powder method gives more precise results for d-spacings and a better separation of the Bragg reflections, although it is less used than the

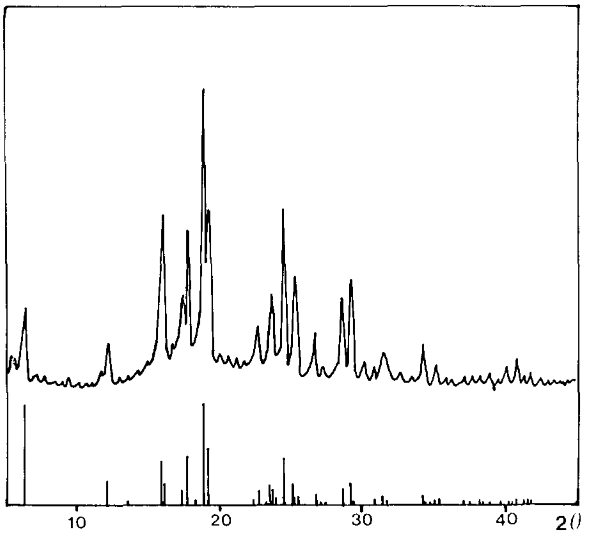

Fig. 1. $I = f(2\theta)$ diffraction spectrum: calculated (lower); observed from micronized sample (upper).

I vs. θ scans. However, the latter may be more appropriate for complementary intensity measurements.

In order to detect possible preferred orientations, a theoretical $I = f(\theta)$ pattern was calculated. Fig. 1 displays that the experimental spectrum of a micronized sample agrees with the calculated one.

Careful comparison of the observed and calculated X-ray diffraction spectra of non-micronized samples shows: (1) supplementary reflections at $\theta = 6.32$, 22.62 and 26.04° on the spectra of some ground samples; and (2) discrepancies between the observed and calculated intensities of the reflections at $\theta = 12.72$, 15.95 and 19.25°. That would indicate the presence of an impurity or a polymorph. But it was verified that these observations are due to remaining preferred orientations since the reflections quoted could be indexed as $h00$ ones ($h = 2$, 4, 5, 6, 7 and 8), in agreement with the crystal packing of the molecules ' that form layers parallel to the (100) face', as quoted by Toffoli et al. (1988). These results allowed us to verify that compression in the same way as for IR spectra does not induce any structural change.

Thus, the IR spectrum reproduced in Fig. 2 may unambiguously be related to the previously determined crystal structure. From this IR spectrum it can be pointed out that:

(a) the 3554 cm^{-1} band may be connected to the stretching of the O–H bond since it disappears on the spectrum of the corresponding STP–O–STP ether-oxide; and (b) the 1001 cm^{-1} band may correspond to the stretching of the C–O– bond (this band moves towards 1018 cm^{-1} when analyzing the corresponding pentane-3-ol).

Thus, it may be concluded that X-ray diffraction and IR studies of STP did not reveal any polymorphism since no unindexed reflection could be observed from analysis of batches recrystallized in various solvents, from which solubility data have been obtained.

The U.V. spectrum of a STP solution in ethanol (1.25×10^{-3} mg/100 ml solution) displays four absorbance maxima at wavelengths close to 306, 268, 262 and 211 nm. The specific absorbance $A_{1\ cm}^{1\%}$ is 580 ± 20 close to 265 nm. These results allowed us to determine the STP solubilities in water, ethanol and chloroform at 25 ± 1 °C. Obtained values were 4.6, 10^4, 3.9×10^4 and 5.0×10^4 mg per 100 ml of saturated solution.

DSC curves show that STP melts at about 75 °C and decomposes at about 190 °C (onset of the exothermic effect). Using a FP800 Mettler thermal analyzer, 11 measurements on 6 batches at heating rates of 5 and 10 K min^{-1} led to a temperature of fusion T_{fus} in the range of 74.5–75.5 °C (onset of the related endothermic effect)

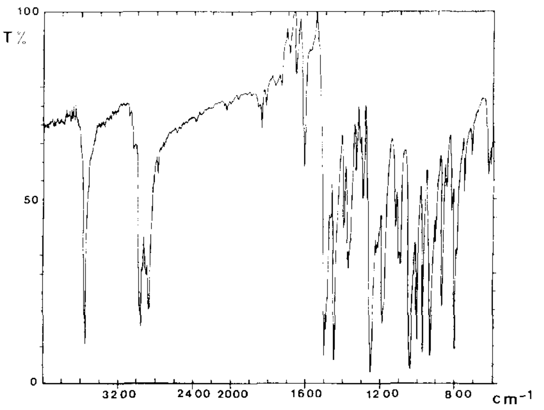

Fig. 2. IR spectrum (Perkin Elmer 580 spectrograph as KBr pellets).

and to an enthalpy of fusion $\Delta_{\mathrm{fus}}\mathrm{H}$ of 29 ± 2 kJ mol^{-1}. Using a TA4000 Mettler thermal analyzer, 7 measurements on 2 batches at heating rates of 1.5 and 10 K min^{-1} led to $\Delta_{\mathrm{fus}}\mathrm{H} = 28 \pm 1$ kJ mol^{-1}.

First assuming the product to be of high purity grade, the curves $\mathrm{T_i}$ versus $1/\mathrm{F_i}$ ($\mathrm{F_i}$ = molten fraction at temperature $\mathrm{T_i}$) were used for determining $\mathrm{T_0}$, the temperature of fusion of the pure compound, using the DTA curves obtained by means of the FP800 analyzer. Graphical representations of $\mathrm{T_i}$ vs. $1/\mathrm{F_i}$ showed that the resulting curves were not straight lines as would be expected from a cryoscopic effect due to an impurity. However, linearity in the area of low $1/\mathrm{F_i}$ values made it possible to estimate $\mathrm{T_0}$ by extrapolation to 75–76 °C. Applying the Sondack method (Sondack, 1972) to the curves obtained using the TA4000 analyzer, purity determinations, on slowly (1.5 K min^{-1}) heated samples of 2 batches, yielded purity values of 99.5–99.8% and $\mathrm{T_0}$ at 75 ± 0.5 °C.

By means of the TA4000 analyzer, crystalline samples of 2 batches were subjected to the following cycles: heating from −100 °C up to 120 °C at 10 K min^{-1}, cooling from 120 °C down to −100 °C at 20 K min^{-1} and heating from −100 °C up to 120 °C at 10 K min^{-1}. Experimental C_p-values were obtained in steps of 5 K for crystalline solid, stable and metastable liquid and glass. Results may be expressed by the linear relationship:

$$C_p/\mathrm{J\ mol^{-1}\ K^{-1}} = \mathrm{A.T/K + B}$$

The following results were found: C_p (crystal) = 0.740 T + 165.9 and C_p (liquid) = 0.529 T + 359.4, in the ranges $218 < \mathrm{T/K} < 338$ and $253 < \mathrm{T/K} < 393$, respectively. Experimental and calculated values agree well for both states. The difference $\Delta C_p = C_p$ (liquid) − C_p (crystal) at $\mathrm{T_{fus}}$ was found to be 120 J mol^{-1} K^{-1}. It confirms a rough value of about 105 J mol^{-1} K^{-1} determined using the FP800 analyzer by comparison with the DTA curve of a substance with known ΔC_p at the fusion (Pindivic et al., 1989).

The molten samples remain in the liquid state after cooling to room temperature. Spontaneous recrystallization of the obtained metastable liquid does not occur within 4 months. When cooled to −100 °C (Fig. 3A) and heated again (Fig. 3B), molten STP undergoes a glass transition: the glass transition $\mathrm{T_g}$ is found in the range $-25 < \mathrm{T_g}/\,°\mathrm{C} < -19$ on heating. The difference $\Delta' C_p = C_p$ (liquid) − C_p (glass) at $\mathrm{T_g}$ is about 110 J mol^{-1} K^{-1}. It should be noted that $\Delta'' C_p = C_p$ (glass) − C_p (crystal) at $\mathrm{T_g}$ is about 40 J mol^{-1} K^{-1}. As observed for annealed glasses (Mazières, 1978), a weak endothermic effect of about 94 J mol^{-1} occurs during heating at the end of the glass transition (Fig. 3B) although the glass was not annealed.

Differential thermal analysis did not reveal any thermal polymorphism from −100 °C up to the fusion. The high purity value obtained for STP from DTA-experiments, as presumed from the

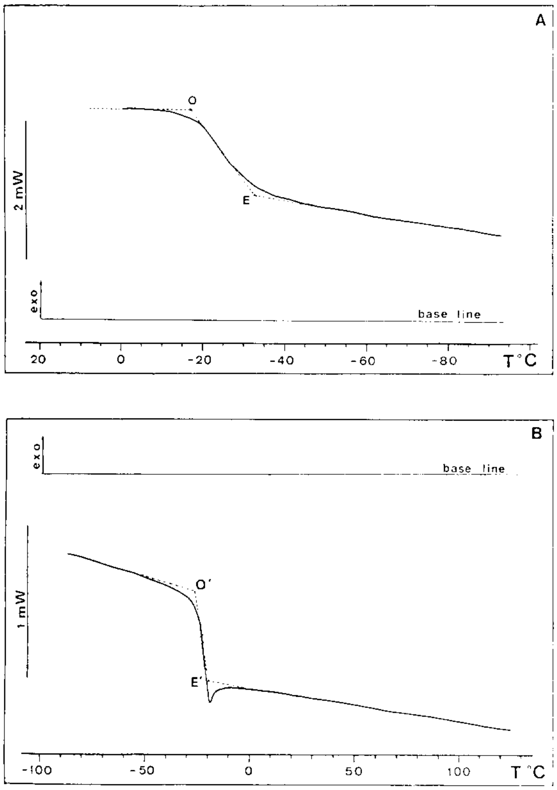

Fig. 3. DTA curves (Mettler TA4000 analyzer). A. Cooling of a molten sample. $\mathrm{T_g}$: onset at −16.8 °C (O), end at −32.5 °C (E). B. Heating of a glassy sample. $\mathrm{T_g}$: onset at −25.9 °C (O′), end at −19.4 °C (E′).

shape of its melting endotherm, was confirmed by chromatographic methods: HPLC studies did not reveal the presence of the Z(±) isomer, that of the STP–O–STP ether-oxide being detected at a concentration lower than 0.25%.

The average value of the enthalpy of fusion allowed us to calculate the entropy of fusion, $\Delta_{fus}S = 84$ J mol^{-1} K^{-1}, which is higher than the empirical one of 56 J mol^{-1} K^{-1} proposed by Walden (see Prigogine and Defay, 1944) for compounds, the molecules of which are neither linear nor globular ones. So, STP may be categorized among the compounds with higher $\Delta_{fus}S$ values (Prigogine and Defay, 1944; Martin, 1973; Jacques et al., 1981).

DTA studies also show that STP may easily be obtained in the glassy state at low temperature: a glass transition was observed at a T_g of about −20 °C. It should be noted that the thus obtained glass would be particularly persistent since T_g and T_{fus} (K) are in the ratio 0.76, which is higher than the one given by the Tamman rule ($T_g/K = 2/3\ T_{fus}/K$). Moreover, this value is one of the highest found for compounds which easily form glasses (Mazières, 1978).

Moreover, it was observed that no recrystallization occurred during heating and that STP remained in the liquid state after it was cooled to room temperature, and stored within 4 months.

The easy formation of a metastable persistent liquid at 25 °C may be connected to the presumed occurrence of a low-temperature metastable eutexy between the STP enantiomers. This hypothesis would agree with the fact that enantiomers have been found to be liquid at room temperature. Using the Prigogine–Defay equation in the form given by Jacques et al. (1981), the racemate-sided liquidus curve of the phase diagram between A and R STP (A = optically active, R = racemate) may be calculated and should be the same as the experimental one since it describes ideal solutions. Calculations indicate that the liquidus at 290 K is made of 99.7 mol% of 1 enantiomer. Thus, the eutectic liquid between A and R could be degenerated on the optically active form.

Experimental studies on this phase diagram are being undertaken in order to check these hypotheses.

Acknowledgment

The authors wish to thank Mr J.M. Ducret, Mettler Instruments S.A. (78220 Viroflay, France), for helpful assistance.

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