

Three new structural forms of thiocolchicoside, a muscle relaxant, as shown by X-ray powder diffraction

R. Toro,¹ J. Contreras,¹ G. Díaz de Delgado,¹ J. M. Delgado,^{1,a)} J.L. Pinto,² and J.A. Henao²

¹Laboratorio de Cristalografía-LNDRX, Departamento de Química, Facultad de Ciencias, Universidad de Los Andes, Mérida 5101, Venezuela

²Grupo de Investigación en Química Estructural (GIQUE), Escuela de Química, Facultad de Ciencias, Universidad Industrial de Santander, A.A. 678, Carrera 27, Calle 9, Ciudadela Universitaria, Bucaramanga, Colombia

(Received 17 June 2013; accepted 28 October 2013)

Thiocolchicoside (THC) is an important active pharmaceutical ingredient (API) used as a muscle relaxant because of its anti-inflammatory and analgesic effects. The only entry for a THC-related compound present in the Cambridge Structural Database (CSD) corresponds to a THC ethanol solvate hydrate (refcode: THCLCS). The diffraction pattern recorded for the THC raw material ($C_{27}H_{33}NO_{10}S \cdot xH_2O$) is different from the pattern calculated using the THCLCS crystallographic data contained in the CSD. The indexing of the THC raw material pattern, produced an orthorhombic unit cell with $a = 28.018(7)$ Å, $b = 12.519(2)$ Å, $c = 8.519(1)$ Å, and $V = 2988.01$ Å³. All the diffraction maxima of the powder pattern of a phase recrystallized in water ($C_{27}H_{33}NO_{10}S \cdot 2H_2O$) can be indexed in an orthorhombic cell with $a = 25.264(4)$ Å, $b = 13.537(3)$ Å, $c = 8.553(1)$ Å, and $V = 2925.12$ Å³. Thermogravimetric analysis shows that this compound is a dihydrate phase. Upon heating, a new anhydrous phase ($C_{27}H_{33}NO_{10}S$) with a monoclinic cell and unit cell parameters: $a = 17.090(5)$ Å, $b = 19.485(5)$ Å, $c = 8.526(3)$ Å, $\beta = 100.30(2)^\circ$, and $V = 2793.34$ Å³ is obtained. © 2013 International Centre for Diffraction Data. [doi:10.1017/S0885715613001383]

Key words: thiocolchicoside, X-ray powder diffraction data, muscle relaxant

I. INTRODUCTION

As part of the work being carried out in our laboratory with the purpose of characterizing common active pharmaceutical ingredients (APIs) and to examine the possible formation of polymorphs under different crystallization conditions, a study by X-ray powder diffraction of thiocolchicoside (THC, Figure 1) was carried out. The chemical nature of the materials and their thermal stability were examined using Fourier transform infrared spectroscopy (FTIR) spectroscopy and thermogravimetric (TGA) and differential scanning calorimetry (DSC) analyses.

THC is a synthetic sulfur derivative of colchicoside used in the symptomatic treatment of painful muscle spasms. Also, pharmacological evidence has shown that under certain conditions, THC induces convulsant activity in animals and humans (Sweetman, 2009). A search in the Cambridge Structural Database V 5.34 (Allen, 2002) for this material produced only one entry for a THC-related compound. It corresponds to a THC ethanol solvate hydrate ($C_{27}H_{33}NO_{10}S \cdot 2C_2H_6O \cdot H_2O$, refcode: THCLCS). The ICDD PDF-4/Organics database (ICDD, 2012) contains its calculated powder diffraction pattern (entry: PDF 02-073-3591).

For the pharmaceutical industry, it is very important to properly characterize the APIs and the excipients, since their different polymorphs and compositions (solvates, anhydrides, etc.) can influence the stability, solubility, bioavailability, and

efficacy of a drug and the manufacturing of the final product (Zhang *et al.*, 2004; Cui, 2007). Polymorphism continues to be an interesting solid state phenomenon, which increasingly attracts a great deal of attention among organic solid state scientists.

II. EXPERIMENTAL

A. Crystallization of THC

Crystallization of raw THC, provided by Laboratorios CAM, Venezuela, was carried out by slow evaporation of a saturated aqueous solution in an oven at 37 °C over a period of 48 h. The light yellow crystals obtained were later subjected to heating at 105 °C for 3 h. Melting points of the raw and the recrystallized materials were determined using an Electrothermal Engineering LTD, model 9100, digital melting point apparatus.

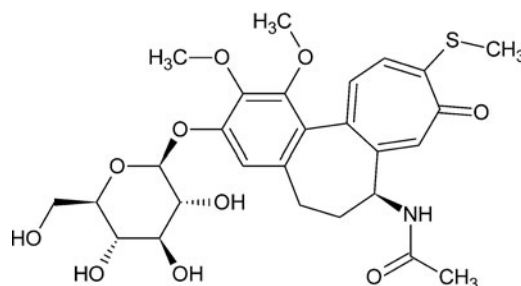


Figure 1. Chemical structure of THC.

^{a)} Author to whom correspondence should be addressed. Electronic mail: miguel@ula.ve

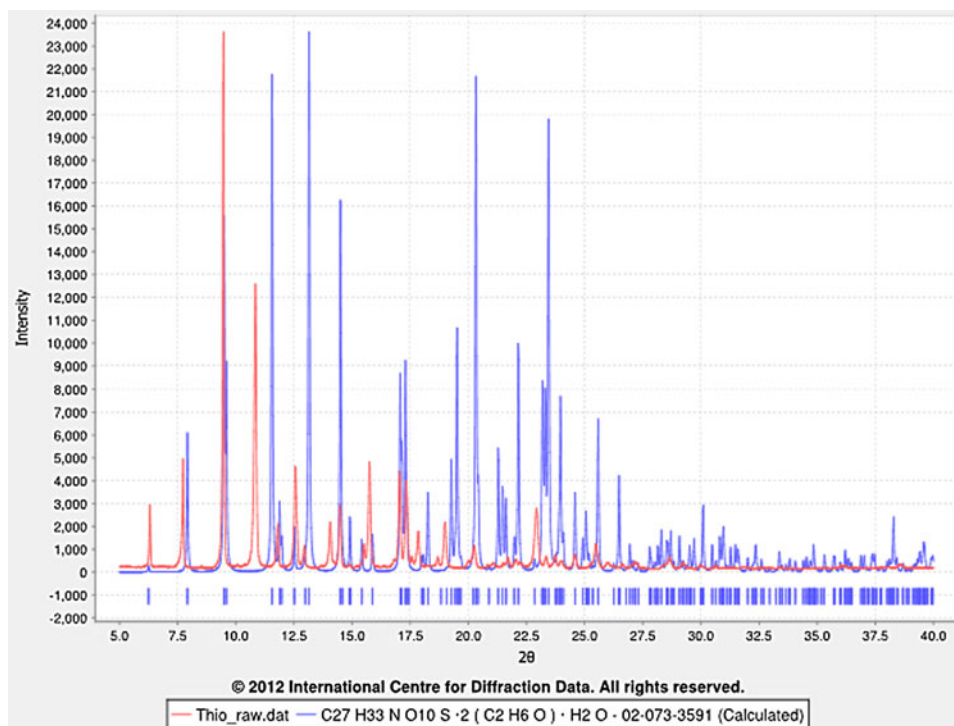


Figure 2. (Color online) Comparison of the powder diffraction pattern of raw THC (red) with PDF 02-073-3591 THCLCS (blue).

TABLE I. X-ray powder diffraction data of raw THC.

No.	$2\theta_{\text{obs}}(^{\circ})$	$d_{\text{obs}}(\text{\AA})$	hkl_o	h	k	l	$2\theta_{\text{calc}}(^{\circ})$	$d_{\text{calc}}(\text{\AA})$	$\Delta(2\theta)$
1	6.308	14.0115	12	2	0	0	6.302	14.0250	-0.006
2	7.729	11.4386	21	1	1	0	7.733	11.4328	0.004
3	9.470	9.3393	100	2	1	0	9.469	9.3399	-0.001
4	10.842	8.1602	53	1	0	1	10.847	8.1561	0.005
5	11.808	7.4946	9	3	1	0	11.813	7.4915	0.005
6	12.564	7.0454	20	0	1	1	12.562	7.0463	-0.002
7	12.948	6.8372	5	1	1	1	12.954	6.8339	0.006
8	14.063	6.2975	9	2	1	1	14.066	6.2963	0.003
9	14.481	6.1165	12	4	1	0	14.477	6.1182	-0.004
10	15.504	5.7153	5	2	2	0	15.501	5.7164	-0.003
11	15.750	5.6264	20	3	1	1	15.748	5.6272	-0.002
12	16.362	5.4172	1	4	0	1	16.368	5.4155	0.005
13	17.045	5.2018	18	3	2	0	17.045	5.2018	0.000
14	17.331	5.1165	17	5	1	0	17.321	5.1195	-0.010
15	17.568	5.0482	3	0	2	1	17.577	5.0456	0.009
16	17.846	4.9702	8	4	1	1	17.845	4.9705	-0.001
17	18.684	4.7491	3	2	2	1	18.689	4.7477	0.005
18	18.995	4.6720	9	4	2	0	19.003	4.6699	0.009
19	20.018	4.4354	2	3	2	1	19.996	4.4403	-0.022
20	20.250	4.3851	5	5	1	1	20.233	4.3889	-0.017
21	20.822	4.2660	1	0	0	2	20.841	4.2622	0.019
22	21.079	4.2147	2	1	0	2	21.083	4.2139	0.004
23	21.246	4.1818	1	5	2	0	21.267	4.1778	0.021
24	21.514	4.1304	2	1	3	0	21.527	4.1279	0.013
25	21.692	4.0968	3	4	2	1	21.698	4.0956	0.006
26	22.038	4.0332	2	0	1	2	22.029	4.0348	-0.009
27	22.217	4.0012	2	2	3	0	22.224	4.0000	0.007
28	22.930	3.8784	12	3	0	2	22.931	3.8783	0.001
29	23.344	3.8105	3	3	3	0	23.341	3.8109	-0.003
30	23.735	3.7486	3	0	3	1	23.737	3.7482	0.003
31	24.003	3.7074	2	3	1	2	24.021	3.7046	0.019
32	24.572	3.6228	3	2	3	1	24.583	3.6211	0.012
33	25.485	3.4950	5	1	2	2	25.480	3.4957	-0.005

Continued

TABLE I. Continued

No.	$2\theta_{\text{obs}}(^{\circ})$	$d_{\text{obs}}(\text{\AA})$	h/l_o	h	k	l	$2\theta_{\text{calc}}(^{\circ})$	$d_{\text{calc}}(\text{\AA})$	$\Delta(2\theta)$
34	25.982	3.4293	2	6	2	1	25.982	3.4293	0.001
35	26.618	3.3488	2	5	3	0	26.621	3.3484	0.003
36	27.087	3.2919	2	3	2	2	27.045	3.2968	-0.041
37	27.198	3.2787	2	5	1	2	27.224	3.2756	0.026
38	28.381	3.1446	1	4	2	2	28.349	3.1481	-0.032
39	28.660	3.1146	3	6	3	0	28.673	3.1133	0.013
40	29.229	3.0553	2	2	4	0	29.234	3.0548	0.004
41	29.531	3.0248	1	9	1	0	29.535	3.0244	0.004
42	29.977	2.9807	2	0	3	2	29.965	2.9819	-0.012
43	30.597	2.9217	1	1	4	1	30.592	2.9222	-0.005
44	31.836	2.8108	2	6	2	2	31.804	2.8136	-0.033
45	33.376	2.6845	1	8	3	0	33.376	2.6845	0.000
46	36.089	2.4887	1	6	4	1	36.105	2.4877	0.016
47	38.557	2.3349	1	8	4	0	38.556	2.3350	-0.001

B. IR spectroscopy and thermal analysis

The FTIR spectra were recorded in KBr pellets, using a Perkin-Elmer PE-1600X spectrophotometer with IRDM software. Thermogravimetric and Derivative Thermogravimetric Analysis (TGA/DTG) and differential scanning calorimetry measurements (DSC) were performed in a thermal analyzer SDT Q600 V3 using 6–7 mg of sample, heating to 600 °C, at a rate of 10 °C min⁻¹, under a dynamic nitrogen atmosphere at 120 ml min⁻¹.

C. X-ray powder diffraction data collection

Powder diffraction patterns were recorded at room temperature on a BRUKER D8 ADVANCE diffractometer working in the Bragg-Brentano geometry using CuK α radiation ($\lambda = 1.54184$ Å), operating at 40 kV and 30 mA. The patterns were recorded in steps of 0.0156° (2θ), from 5° to 60° at 4 s step⁻¹. The diffractometer was equipped with the primary and secondary Soller slits of 2.5°, divergence slit of 0.2 mm, Ni filter of 0.02 mm, and a LynxEye detector. The profile fit of each pattern was carried out with the FULLPROF software (Rodriguez-Carvajal, 1990). The indexing of each pattern was performed with the program DICVOL06 (Boultif and

Louer, 2004) and analyzed with the NBS*AIDS83 program (Mighell *et al.*, 1981).

III. RESULTS

The crystallization experiments carried out on raw THC led to two new phases: a dihydrated phase and an anhydrous phase obtained after heating the dihydrate. For the sake of clarity, the results of the characterization of each of these materials are presented separately in the following paragraphs.

A. Raw THC

The FTIR spectrum of raw THC clearly shows the chemical nature of the compound under study. The bands corresponding to the -OH stretching appear at 3421 cm⁻¹ and the N-H stretching of the secondary amide appears at 3300 cm⁻¹. In general, the spectrum shows broad absorption bands possibly because of the large number of hydrogen bonds present.

This phase exhibits an endothermic transition at 51.86 °C and melts and immediately decomposes at 204–206 °C, according to the DSC analysis. The TGA curve shows that this material undergoes a weight loss of 5.524% at 51.86 °C, consistent with the endotherm observed in DSC analysis. The low peak temperature of this process seems to indicate the presence of moisture in the sample and the percentage suggests a degree of hydration greater than one but less than two water molecules. A weight loss of 53%, attributed to the decomposition of the material, occurs above 210 °C.

The powder diffraction pattern recorded for the raw material (THC) does not match the pattern for THCLCS contained in the PDF-4/Organics database (Figure 2). The indexing of this pattern carried out with DICVOL06 and the analysis of 47 diffraction maxima recorded, performed with NSB*AIDS83, led to an orthorhombic unit cell with $a = 28.018(7)$ Å, $b = 12.519(2)$ Å, $c = 8.519(1)$ Å, and $V = 2988.01$ Å³. The Miller indices of the reflections suggest P2₁2₁2₁ as possible space group. The de Wolf (de Wolf, 1968) and Smith–Snyder (Smith and Snyder, 1979) figures of merit obtained were $M_{20} = 56.5$ and $F_{20} = 137.6$ (0.0035, 42), respectively. Table I contains the corresponding powder diffraction data. The fitting of the whole pattern with the Le Bail algorithm implemented in FULLPROF (Rodriguez-Carvajal, 1990), in space group P2₁2₁2₁, accounts for all the diffraction maxima

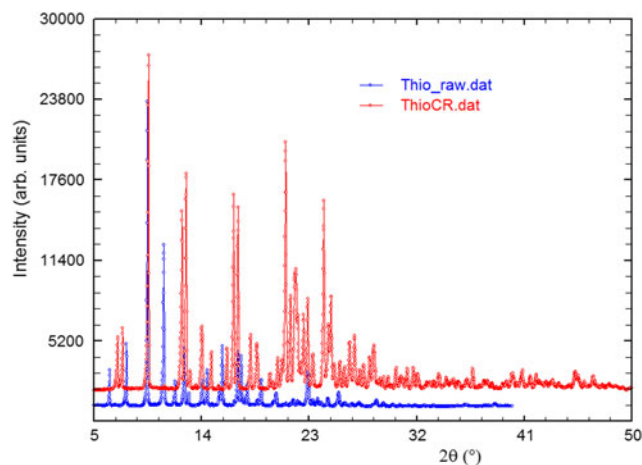


Figure 3. (Color online) Comparison of the powder diffraction pattern of the recrystallized material (red) with the pattern recorded for raw THC (blue).

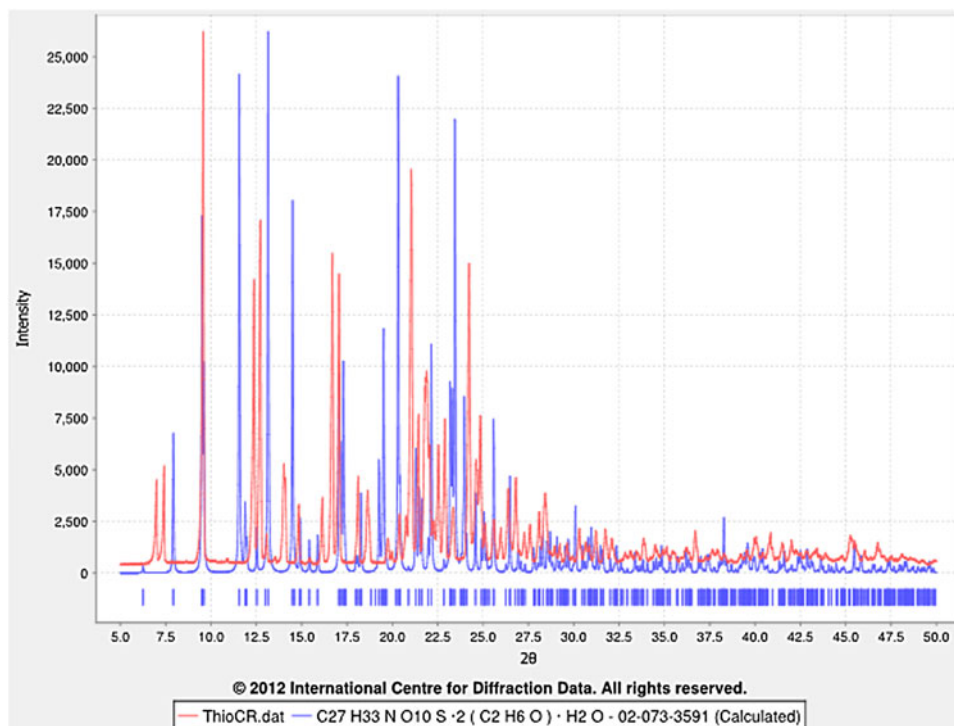


Figure 4. (Color online) Comparison of the powder diffraction pattern of recrystallized THC (red) with PDF 02-073-3591 THCLCS (blue).

TABLE II. X-ray powder diffraction data of THC recrystallized in water.

No.	$2\theta_{\text{obs}}(^{\circ})$	$d_{\text{obs}}(\text{\AA})$	h	k	l	$2\theta_{\text{calc}}(^{\circ})$	$d_{\text{calc}}(\text{\AA})$	$\Delta(2\theta)$
1	6.985	12.6539	17	2	0	6.990	12.6463	0.004
2	7.401	11.9451	19	1	0	7.403	11.9405	0.003
3	9.564	9.2472	100	2	0	9.568	9.2436	0.004
4	12.363	7.1593	53	3	0	12.366	7.1576	0.003
5	12.714	6.9626	65	1	1	12.722	6.9583	0.008
6	13.068	6.7745	7	0	2	13.072	6.7724	0.004
7	14.019	6.3169	20	4	0	14.006	6.3231	-0.014
8	14.105	6.2786	17	2	1	14.099	6.2816	-0.007
9	14.835	5.9714	12	2	0	14.838	5.9702	0.003
10	16.135	5.4930	14	3	1	16.139	5.4916	0.004
11	16.686	5.3131	59	0	2	16.690	5.3118	0.004
12	17.054	5.1992	54	1	2	17.056	5.1984	0.003
13	18.110	4.8984	18	2	1	18.114	4.8973	0.004
14	18.636	4.7613	15	4	1	18.633	4.7618	-0.002
15	19.750	4.4950	6	3	2	19.754	4.4942	0.004
16	20.389	4.3556	10	5	0	20.391	4.3553	0.002
17	20.753	4.2801	11	0	2	20.747	4.2812	-0.005
18	21.042	4.2220	74	1	0	21.046	4.2212	0.004
19	21.432	4.1459	29	5	1	21.431	4.1462	-0.001
20	21.784	4.0798	35	0	2	21.771	4.0821	-0.013
21	21.884	4.0614	37	4	1	21.852	4.0671	-0.032
22	22.264	3.9929	10	0	3	22.259	3.9938	-0.005
23	22.537	3.9451	23	1	3	22.538	3.9449	0.001
24	22.891	3.8849	28	2	2	22.892	3.8848	0.000
25	23.346	3.8102	12	2	3	23.357	3.8084	0.011
26	24.224	3.6741	56	3	2	24.223	3.6741	0.000
27	24.622	3.6155	21	0	2	24.600	3.6188	-0.022
28	24.847	3.5833	29	1	2	24.854	3.5823	0.007
29	25.111	3.5463	9	4	0	25.119	3.5451	0.009
30	25.597	3.4800	10	2	2	25.603	3.4791	0.007
31	25.979	3.4297	8	4	2	25.980	3.4295	0.001

Continued

TABLE II. Continued

No.	$2\theta_{\text{obs}}(^{\circ})$	$d_{\text{obs}}(\text{\AA})$	h	k	l	$2\theta_{\text{cal}}(^{\circ})$	$d_{\text{calc}}(\text{\AA})$	$\Delta(2\theta)$
32	26.393	3.3768	15	4	3	26.395	3.3766	0.002
33	26.805	3.3259	17	3	2	26.809	3.3254	0.004
34	27.275	3.2696	7	2	4	27.263	3.2710	-0.012
35	27.588	3.2332	9	7	1	27.592	3.2328	0.003
36	28.093	3.1762	11	5	1	28.088	3.1768	-0.005
37	28.424	3.1399	15	4	2	28.417	3.1408	-0.008
38	29.228	3.0554	5	2	4	29.226	3.0556	-0.002
39	29.619	3.0159	5	2	3	29.609	3.0169	-0.010
40	30.305	2.9492	8	3	4	30.298	2.9499	-0.007
41	31.226	2.8643	8	8	2	31.221	2.8648	-0.005
42	31.740	2.8191	8	4	4	31.744	2.8187	0.004
43	32.104	2.7880	6	4	3	32.100	2.7883	-0.004
44	32.835	2.7276	4	2	1	32.841	2.7271	0.006
45	33.116	2.7050	4	7	1	33.109	2.7056	-0.007
46	33.438	2.6798	4	7	3	33.442	2.6794	0.005
47	33.856	2.6476	6	5	3	33.861	2.6473	0.004
48	34.482	2.6009	5	4	0	34.476	2.6014	-0.006
49	35.125	2.5548	5	4	1	35.126	2.5547	0.001
50	35.406	2.5351	4	3	4	35.435	2.5332	0.029
51	36.170	2.4834	5	9	2	36.159	2.4841	-0.010
52	36.702	2.4486	8	4	4	36.701	2.4487	-0.001
53	37.576	2.3936	4	4	5	37.618	2.3910	0.042
54	37.897	2.3740	4	7	4	37.899	2.3739	0.002
55	39.223	2.2968	3	9	3	39.196	2.2983	-0.027
56	39.504	2.2811	4	1	5	39.526	2.2799	0.022
57	40.027	2.2525	6	2	5	40.026	2.2526	-0.001
58	40.846	2.2092	7	3	5	40.846	2.2092	0.000
59	41.473	2.1772	5	11	2	41.473	2.1773	0.000
60	42.008	2.1507	6	2	4	42.012	2.1506	0.004
61	43.402	2.0849	5	2	1	43.390	2.0854	-0.012
62	45.250	2.0039	7	5	4	45.252	2.0038	0.002
63	46.737	1.9436	6	3	6	46.748	1.9431	0.012

recorded. The X-ray powder diffraction data along with the FTIR and thermal analysis results indicate that this material is a previously unreported THC phase.

B. THC recrystallized in water

The bands observed in the FTIR spectrum of this phase are better defined than those of the raw sample. Two -OH stretches appear at 3548 and 3434 cm^{-1} . The first band at 3548 cm^{-1} corresponds to a water molecule, whereas the 3434 cm^{-1} band corresponds to the -OH groups of the glucoside residue. The N-H stretching appears at 3250 cm^{-1} .

The TGA curve shows that, at about 50 $^{\circ}\text{C}$, this material begins to lose weight (6.125%, corresponding to the loss of two water molecules) with a peak temperature (T_p) of 79.89 $^{\circ}\text{C}$. This endothermic process is observed in the DSC at a peak temperature of 79.24 $^{\circ}\text{C}$. DSC also shows that this phase melts at 269 $^{\circ}\text{C}$, and undergoes decomposition between \sim 280 and 600 $^{\circ}\text{C}$ (weight loss of 54.25% and $T_p = 307.32$ $^{\circ}\text{C}$). It is worth noting that this behavior is different from the thermal behavior of raw THC.

The crystals obtained were irregularly shaped blocks of size and quality appropriate for single crystal X-ray diffraction analysis. The crystal structure of this dihydrated phase was determined and will be reported elsewhere.

The powder diffraction pattern recorded for this phase is different from the one recorded for the raw material

(Figure 3) and from the one reported for THCLCS in PDF-4/Organics (Figure 4). The indexing of the pattern carried out using DICVOL06 produced an orthorhombic unit cell. The analysis of the entire pattern (63 diffraction maxima) with NBS*AIDS83 resulted in a unit cell with parameters: $a = 25.264(4)$ \AA , $b = 13.537(3)$ \AA , $c = 8.553(1)$ \AA , and $V = 2925.12$ \AA^3 . The set of reflections observed are consistent with space group $P2_12_12_1$ obtained in the single-crystal analysis. The de Wolf (de Wolf, 1968) and Smith-Snyder (Smith and Snyder, 1979) figures of merit obtained were $M_{20} = 47.3$ and $F_{20} = 131.2$ (0.0040, 38), respectively. The powder diffraction data are presented in Table II.

C. Dehydrated THC obtained from the recrystallized phase

The dihydrate THC phase obtained by recrystallization in water was heated at 105 $^{\circ}\text{C}$ for 3 h. A change in the morphology of the crystals upon heating, from blocks to an opaque yellow powder, was observed.

The FTIR spectrum recorded for this material differs slightly from those previously obtained. The absorption bands observed are generally broad. The -OH stretching vibration appears at 3435 cm^{-1} , whereas the N-H stretch appears at 3324.54 cm^{-1} . DSC curves show an endothermic transition at 264.31 $^{\circ}\text{C}$ corresponding to melting, followed by decomposition at $T_p = 338.65$ $^{\circ}\text{C}$.

TABLE III. X-ray powder diffraction data of the recrystallized THC after heating.

No.	$2\theta_{\text{obs}}(^{\circ})$	$d_{\text{obs}}(\text{\AA})$	$h/k/l$	h	k	l	$2\theta_{\text{cal}}(^{\circ})$	$d_{\text{cal}}(\text{\AA})$	$\Delta(2\theta)$
1	6.947	12.7239	100	-1	1	0	6.944	12.7301	-0.003
2	9.072	9.7477	26	0	2	0	9.077	9.7423	0.005
3	10.493	8.4306	47	1	2	0	10.494	8.4297	0.001
4	10.912	8.1078	5	-1	0	1	10.913	8.1073	0.001
5	11.464	7.7186	10	2	1	0	11.463	7.7196	-0.001
6	11.823	7.4850	7	-1	1	1	11.823	7.4852	0.000
7	12.595	7.0279	3	1	0	1	12.606	7.0217	0.011
8	13.408	6.6036	11	1	1	1	13.403	6.6059	-0.005
9	13.918	6.3627	25	-2	2	0	13.913	6.3651	-0.005
10	14.241	6.2191	11	-2	1	1	14.260	6.2108	0.019
11	14.613	6.0616	61	-1	3	0	14.620	6.0586	0.007
12	15.557	5.6959	5	1	2	1	15.556	5.6963	-0.001
13	16.212	5.4672	20	2	0	1	16.205	5.4696	-0.007
14	17.381	5.1020	14	-3	0	1	17.386	5.1005	0.005
15	18.229	4.8665	11	0	4	0	18.212	4.8711	-0.017
16	18.608	4.7683	12	1	3	1	18.609	4.7679	0.001
17	18.967	4.6788	9	1	4	0	18.967	4.6788	0.000
18	19.646	4.5186	8	-3	2	1	19.646	4.5187	0.000
19	20.563	4.3191	3	3	0	1	20.570	4.3176	0.007
20	20.937	4.2428	11	-3	3	0	20.934	4.2434	-0.003
21	21.152	4.2002	13	4	0	0	21.134	4.2038	-0.018
22	21.388	4.1544	15	-1	1	2	21.389	4.1541	0.001
23	21.645	4.1056	9	-4	1	0	21.626	4.1093	-0.019
24	22.196	4.0049	10	1	4	1	22.210	4.0023	0.014
25	22.410	3.9672	9	-2	1	2	22.401	3.9687	-0.009
26	22.825	3.8960	12	-1	2	2	22.819	3.8969	-0.006
27	23.749	3.7464	8	-4	2	1	23.741	3.7477	-0.008
28	24.207	3.6766	8	-3	4	0	24.206	3.6767	-0.001
29	24.529	3.6290	14	1	2	2	24.538	3.6277	0.009
30	25.263	3.5252	14	0	3	2	25.276	3.5234	0.013
31	25.863	3.4448	8	-4	3	1	25.878	3.4428	0.015
32	26.507	3.3626	10	5	0	0	26.503	3.3631	-0.004
33	26.900	3.3143	4	5	1	0	26.902	3.3140	0.002
34	27.473	3.2465	10	0	6	0	27.465	3.2474	-0.008
35	28.070	3.1788	9	5	2	0	28.068	3.1790	-0.002
36	28.837	3.0960	3	-3	5	1	28.831	3.0966	-0.006
37	29.911	2.9872	4	5	3	0	29.919	2.9864	0.008
38	31.384	2.8503	8	4	4	1	31.382	2.8504	-0.002
39	31.805	2.8135	5	-6	0	1	31.805	2.8135	0.000
40	32.321	2.7697	4	-5	2	2	32.334	2.7686	0.013
41	33.205	2.6980	3	-2	2	3	33.205	2.6980	0.000
42	33.982	2.6381	3	-5	3	2	33.974	2.6386	-0.008
43	34.866	2.5732	4	-6	3	0	34.866	2.5732	0.000
44	35.563	2.5243	3	6	0	1	35.540	2.5259	-0.023
45	37.009	2.4290	4	-6	4	0	37.005	2.4292	-0.004
46	37.732	2.3841	3	7	1	0	37.731	2.3841	-0.001
47	38.616	2.3315	4	7	2	0	38.602	2.3323	-0.014
48	41.913	2.1554	3	-7	4	0	41.932	2.1544	0.019
49	43.420	2.0840	3	0	1	4	43.397	2.0851	-0.023
50	44.866	2.0202	4	-2	3	4	44.859	2.0205	-0.007
51	45.308	2.0015	4	2	8	2	45.315	2.0012	0.007

The entire powder diffraction pattern registered is consistent with the monoclinic unit cell found by DICVOL06 for the first 20 peaks used in the indexing process. The unit cell parameters obtained with NBS*AIDS83, after the analysis of the 51 diffraction maxima recorded, are: $a = 17.090(5)$ Å, $b = 19.485(5)$ Å, $c = 8.526(3)$ Å, $\beta = 100.30(2)^{\circ}$, and $V = 2793.34$ Å³. The indices of the reflections observed are consistent with $P2_1$ as possible space group. The de Wolf (de Wolf, 1968) and Smith–Snyder (Smith and Snyder, 1979) figures of merit obtained were $M_{20} = 36.6$ and $F_{30} = 56.3$ (0.0067, 79), respectively (see Table III).

A comparison of the powder diffraction pattern of raw THC, the pattern of the material recrystallized in water and the pattern of the dehydrated phase, obtained from the recrystallized material after heating (shown in Figure 5), clearly indicates that THC exhibits several solvates and polymorphic modifications that, to our knowledge, have not been previously reported.

Given the interesting behavior observed for THC, additional experiments are being carried out in order to examine the possible interconversions among its crystalline phases.

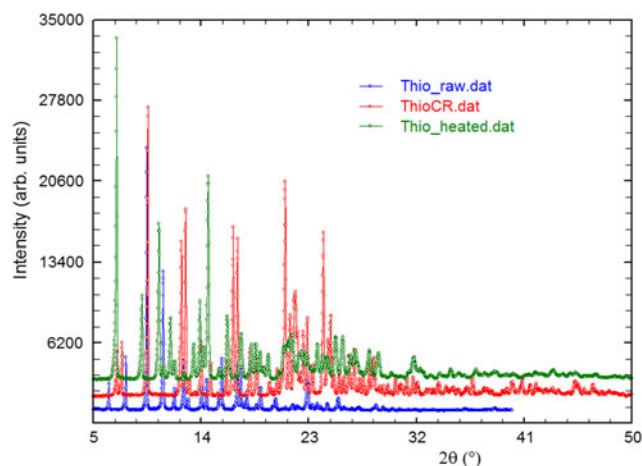


Figure 5. (Color online) Comparison of the powder diffraction pattern of raw THC (blue) with the pattern of the recrystallized material (red) and the pattern of the heated recrystallized THC (green).

ACKNOWLEDGMENTS

This work was made possible thanks to the grant LAB-97000821 from FONACIT-Venezuela for Laboratorio de Cristalografía-LNDRX and a grant for Laboratorio de Difracción de Rayos-X, PTG, Universidad Industrial de Santander, Bucaramanga, Colombia. The authors thank

Marlin Villarroel for technical assistance with the TGA/DSC analysis.

- Allen, F. H. (2002). "The Cambridge Structural Database: a quarter of a million crystal structures and rising." *Acta Crystallogr., Sect. B: Struct. Sci.* **58**, 380–388.
- Boultif, A. and Louer, D. (2004). "Powder pattern indexing with the dichotomy method," *J. Appl. Crystallogr.* **37**, 724–731.
- Cui, Y. (2007). "A material science perspective of pharmaceutical solids," *Int. J. Pharm.* **339**, 3–18.
- de Wolff, P. M. (1968). "A simplified criterion for the reliability of a powder pattern indexing," *J. Appl. Crystallogr.* **1**, 108–113.
- ICDD (2012). PDF-4/Organics 2012 (Database), edited by S. Kabekkodu, International Centre for Diffraction Data, Newtown Square, PA, USA.
- Mighell, A. D., Hubbard, C. R., and Stalick, J. K. (1981). *NBS* AIDS80: A Fortran Program for Crystallographic Data Evaluation*. USA: National Bureau Standards, Technical Note 1141. (*NBS* AIDS83* is a newer version of *NBS* AIDS80*).
- Rodriguez-Carvajal, J. (1990). "FULLPROF: a program for Rietveld refinement and pattern matching analysis," in *Abstracts of the Satellite Meeting on Powder Diffraction of the XV Congress of the IUCr*, Toulouse, France, p. 127.
- Smith, G. S. and Snyder, R. L. (1979). "FN: a criterion for rating powder diffraction patterns and evaluating the reliability of powder-pattern indexing," *J. Appl. Crystallogr.* **12**, 60–65.
- Sweetman S. C. (Ed.) (2009). *Martindale: The Complete Drug Reference*. (Pharmaceutical Press, London), 36th ed., p. 1120.
- Zhang, G. G. Z., Law, D., Schmitt, E. A., and Qiu, Y. (2004). "Phase transformation considerations during process development and manufacture of solid oral dosage forms," *Adv. Drug Deliv. Rev.* **56**, 371–390.