J Therm Anal Calorim (2010) 102:163–170
DOI 10.1007/s10973-010-0939-x

Thermoanalytical study of some anti-inflammatory analgesic agents

G. Bannach · R. Arcaro · D. C. Ferroni · A. B. Siqueira · O. Treu-Filho · M. Ionashiro · E. Schnitzler

Received: 30 July 2009 / Accepted: 21 June 2010 / Published online: 6 July 2010

Abstract Thermogravimetry (TG), differential thermal analysis (DTA), differential scanning calorimetry (DSC) as well as X-ray diffraction powder (DRX) patterns and Fourier transformed infrared spectroscopy (FTIR) were used to study ketoprofen, ibuprofen, and naproxen. The chemical or physical properties of the studied compounds were established and when possible by X-ray powder diffractometry and/or infrared spectroscopy were used. In this investigation, quantum chemical approach was used to determine the molecular structures using Becke three-parameter hybrid method and the Lee–Yang–Par (LYP) correlation functional. The performed molecular calculations in this work were done using the Gaussian 03 routine. Theoretical calculations help in interpretations of FTIR spectra supplying structural and physicochemical parameters.

G. Bannach (✉)
Falculdade de Ciências – UNESP – Departamento de Química, Buru, SP CEP 17033-260, Brazil
e-mail: gilbert@fc.unesp.br

R. Arcaro · D. C. Ferroni · E. Schnitzler
Universidade Estadual de Ponta Grossa – Depto. Química, Ponta Grossa, PR CEP 84030-900, Brazil

A. B. Siqueira
Universidade Federal do Mato Grosso, Pontal do Araguaia, MT CEP 78698-000, Brazil

O. Treu-Filho · M. Ionashiro
Instituto de Química de Química – UNESP, Araraquara, SP CEP 14800-900, Brazil

Keywords Ketoprofen · Ibuprofen · Naproxen · Thermal behavior · Infrared spectroscopy · Theoretical calculations

Introduction

Thermal methods of analysis are widely used for checking thermal decomposition, thermal stability [1–4], polymorphism [2], reactions in solid state, drug formulations [5–8], purity [9], and other properties of solid compounds used in pharmaceutical industry [1, 5, 9–12]. Because of the numerous issues involved, it becomes important to have a complete understanding of the properties of pharmaceutical materials.

A pharmaceutical preparation consists of the actual drug(s) or active ingredient(s) together with so-called excipients or inactive ingredients (fillers, additives, etc.), all of which must be present in the correct proportions. Pharmaceutical preparations [13–16] provide the means by which pharmaceutically active substances or drugs can be supplied to the body, so that both the physiological considerations concerning the means of application (oral, cutaneous, sub-cutaneous, and rectal, etc.) and the physico-chemical properties of the drug are suitable.

Micro-thermal analysis has been applied as a means in situ characterization of ibuprofen pharmaceutical tablet coat [17]. Thermal studies with ibuprofen [18] and its mixtures with starch [15] were realized. DSC was used as a screening technique to determine the compatibility of ketoprofen with excipients [19]. Studies with mixtures of naproxen in binary or ternary solid dispersions were also described [20–22], as well as theoretical calculations in structural investigations [23].

No reference has been found on the application of TG–DTA and DSC in the comparative study and thermal behavior of these compounds.

Experimental

The analgesic and anti-inflammatory drugs: ketoprofen (lot. 3713), ibuprofen (lot. 3712) and naproxen (lot. no. 7210) were furnished by Geabras Prod. Quím. Farm. Ltd. The structural formula is shown in Fig. 1.

Simultaneous TG–DTA curves were obtained with thermal analysis system, model SDT 2960 (TA Instruments). The purge gas was an air flow of 100 mL min^{-1}. A heating rate of 20 °C min^{-1} was adopted, with samples weighing about 4–5 mg. Alumina crucible was used for TG–DTA curves.

DSC curves (heating and cooling) were obtained with thermal analysis systems model Q-10 (TA Instruments). The purge gas was an air flow of 100 mL min^{-1}. A heating rate of 20 °C min^{-1} was adopted with samples weighing about 2.5 mg. Aluminum crucibles, with perforated cover, were used for recording the DSC curves. The determination of purity is based on the assumption that an impurity will depress the melting point of a pure material whose melting is characterized by melting point.

X-ray powder patterns were obtained by using a Siemens D-5000 X-ray diffractometer, employing Cu Kα radiation ($\lambda = 1.541$ Å) and settings of 40 kV and 20 mA.

Infrared spectra for these compounds were run on a spectrophotometer model FTIR-8400 (Shimadzu), within the 4000–400 cm^{-1} range. The solid samples were pressed into KBr pellets or directly by reflectance.

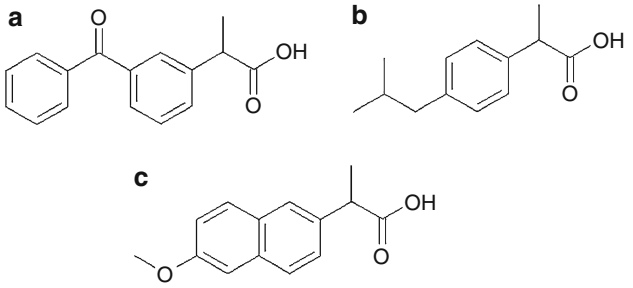

Fig. 1 Structural formulas of **a** ketoprofen, **b** ibuprofen, and **c** naproxen

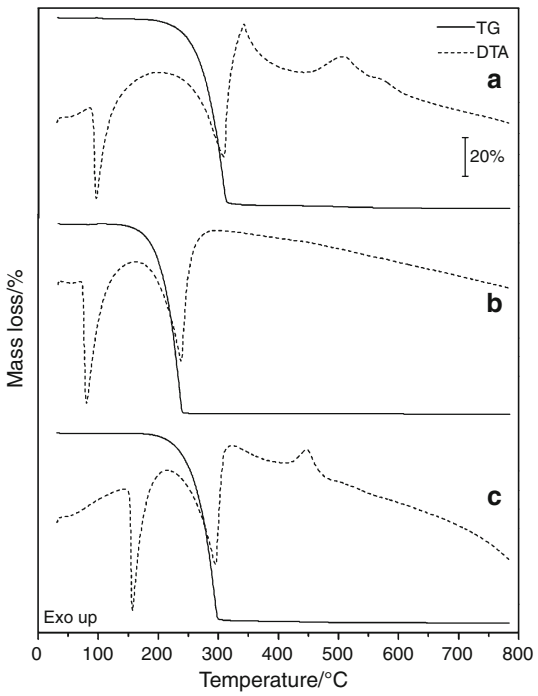

Fig. 2 TG–DTA curves *a* ketoprofen ($m = 4.757$ mg), *b* ibuprofen ($m = 5.173$ mg), *c* naproxen ($m = 4.942$ mg)

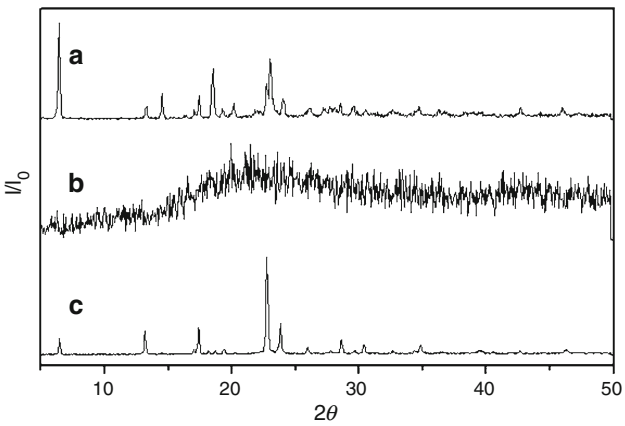

Fig. 3 X-ray diffraction powder patterns of ketoprofen: *a* solid, *b* melting, and *c* recrystallized

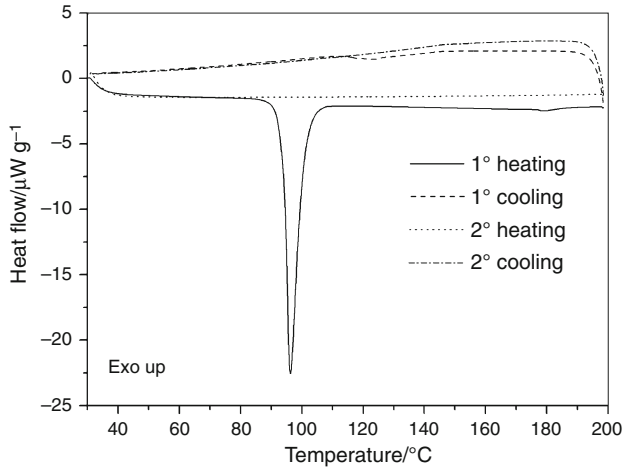

Fig. 4 DSC curve of ketoprofen (heating and cooling); $m = 2.676$ mg

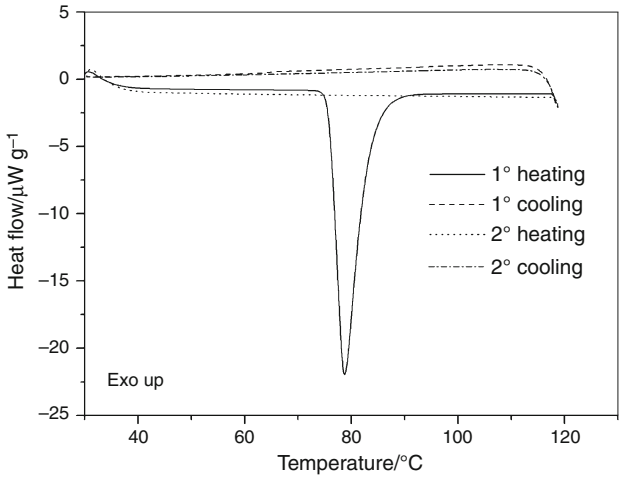

Fig. 5 DSC curve of ibuprofen (heating and cooling); $m = 2.448$ mg

Computational Strategy

In this investigation, the employed quantum chemical approach to determining the molecular structures was Becke three-parameter hybrid method [24] using the Lee–Yang–Par (LYP) correlation functional [25] and the basis sets used for calculations were the 6-311g(d) [26, 27]. The performed molecular calculations in this work were done using the Gaussian 03 routine [28].

As the molecular structure of the compounds could not be determined by the single crystal X-ray diffraction technique, a geometry optimization was computed using the optimized algorithm of Berny [29].

The theoretical infrared spectrum, it was calculated using a harmonic field [30] based on C_1 symmetry (electronic state ^{1}A). Frequency values (not scaled), relative intensities, assignments and description of vibrational modes are presented. The calculations of vibrational frequencies were also implemented to determine see an optimized geometry constitutes minimum or saddle points. The principal infrared-active fundamental modes assignments and descriptions were done by the GaussView 3.0 graphics routine [31].

Results and discussion

The thermal behavior of the drug substances is shown in Fig. 2a–c. TG–DTA curves of ketoprofen show thermal stability until 170 °C. The first mass loss occurs between 170 and 378 °C with loss of 98.5% corresponding to an endothermic peak at 309 °C and an exothermic peak at 343 °C. The second mass loss occurs between 435 and 617 °C with loss of 1.5%, corresponding to an exotherm between 444 and 611 °C. The melting of the compound begins at 86 °C with peak at 97 °C, in agreement with the literature [13]. However, it was observed that the ketoprofen once melted do not returns to solid state, even after 12 h except by external interaction. X-ray powder patterns of the ketoprofen, melted, and recrystallized by external interaction are shown in Fig. 3. The break in the TG curve between 92 and 114 °C is attributed to the melting of the sample.

Table 1 Infrared spectroscopic theoretical and experimental data of ketoprofen, ibuprofen, and naproxen

Compound	Ketoprofen			Ibuprofen			Naproxen		
IR data (cm^{-1})	ν Theor.	ν Exp.	$\Delta\nu$/%	ν Theor.	ν Exp.	$\Delta\nu$/%	ν Theor.	ν Exp.	$\Delta\nu$/%
C–H aromatic stretch	3186	3053	+4.36	3160	3094	+2.13	3165	3000	+5.50
CH_3 antisymm. stretch	3111	2981	+4.36	3083	2955	+4.33	3104	2968	+4.58
CH_2 antisymm. stretch	–	–	–	3051	2922	+4.41	–	–	–
C=O carboxylic acid stretch	1821	1697	+7.31	1824	1718	+6.40	1828	1726	+5.91
C=O ketone stretch	1724	1654	+4.23	–	–	–	–	–	–
Symm. ring strech	1645, 1625	1593	+3.26	1550	1508	+2.78	1678, 1653	1603	+4.68
CH_3 asymmetric bend	1519	1448	+4.90	1517	1458	+4.05	1522	1458	+4.39
C–C–O–H antisymm. bend/stretch	1405	1417	−0.85	1360	1419	−4.16	1359	1392	−2.37
CH_3 symmetric bend	1430	1373	+4.15	1414	1373	−2.99	1428	–	–
C–O–C asymm. stretch methoxy group	–	–	–	–	–	–	1305	1226	+6.44
C–O–C symm. stretch methoxy group	–	–	–	–	–	–	1070	1026	+4.29
C–C–C stretch/bend ketone group	1293	1283	+0.78	–	–	–	–	–	–
C–C–O antisymm. bend/stretch	–	–	–	1197	1267	−5.52	210	1267	+4.50
OH out-of-plane in acid dimer	–	–	–	–	939	–	–	924	–
Symm. out-of-plane ring hydrogens	736	712	+3.37	793	744	+6.58	808	796	+1.51
Out-of-plane ring bend	706	698	+1.15	661	669	−1.20	684	671	+1.94

Table 2 Theoretical data of geometry 3D of ketoprofen structure of Fig. 6

Atom no.	Atom symbol	NA	NB	NC	Bond/Å	Angle/degree	Dihedral/degree	*X*/Å	*Y*/Å	*Z*/Å
1	C							3.480146	−1.363471	−0.254121
2	O	1			1.205074			4.599556	−1.026627	−0.546799
3	O	1	2		1.353008	122.550448		2.814772	−2.335280	−0.920076
4	H	3	1	2	0.970052	107.081127	−1.492198	3.396258	−2.641005	−1.633804
5	C	1	2	3	1.522427	125.801359	−178.40816	2.628427	−0.757418	0.852703
6	H	5	1	2	1.092589	106.985488	−151.56861	1.939873	−1.536467	1.188452
7	C	5	1	2	1.535245	110.773355	−33.164966	3.505535	−0.303833	2.028254
8	H	7	5	1	1.090354	111.090751	58.873557	4.242166	0.432973	1.706753
9	H	7	5	1	1.091833	110.098849	179.084643	2.885856	0.143397	2.808050
10	H	7	5	1	1.092899	110.970746	−60.918471	4.047420	−1.148668	2.460738
11	C	5	1	2	1.527006	108.967508	91.212334	1.794236	0.381162	0.270030
12	C	11	5	1	1.395861	120.246837	121.590309	0.401299	0.346232	0.353299
13	C	11	5	1	1.398728	120.958958	−59.249144	2.405250	1.482270	−0.338790
14	C	12	11	5	1.400195	121.149741	178.005795	−0.380258	1.399213	−0.137564
15	H	12	11	5	1.084440	119.176090	−0.355095	−0.078680	−0.500865	0.830852
16	C	13	11	5	1.393692	120.496751	−177.75617	1.636653	2.537932	−0.825836
17	H	13	11	5	1.085176	119.700932	2.592865	3.485557	1.511350	−0.437273
18	C	16	13	11	1.389131	120.290132	−0.058201	0.252472	2.507334	−0.712730
19	H	16	13	11	1.085142	119.725808	179.652185	2.124088	3.388635	−1.290857
20	H	18	16	13	1.083652	121.175923	178.396739	−0.357365	3.331703	−1.063180
21	C	14	12	11	1.501872	122.762708	−176.53964	−1.875342	1.434672	0.000592
22	O	21	14	12	1.219189	119.704303	148.485562	−2.446657	2.506094	0.110477
23	C	21	14	12	1.501016	120.385130	−31.689430	−2.668291	0.160199	0.000093
24	C	23	21	14	1.401080	123.020997	−29.736789	−2.263218	−0.990790	−0.688503
25	C	23	21	14	1.401832	117.787099	154.454477	−3.909760	0.162677	0.651154
26	C	24	23	21	1.393126	120.323431	−176.29555	−3.080063	−2.119018	−0.714310
27	H	24	23	21	1.083787	120.117629	2.092907	−1.322670	−0.999649	−1.226913
28	C	25	23	21	1.388843	120.530450	177.552419	−4.713277	−0.970093	0.642392
29	H	25	23	21	1.083797	118.490898	−2.152758	−4.227480	1.068095	1.155028
30	C	26	24	23	1.392845	120.115858	−0.724188	−4.299754	−2.114284	−0.041741
31	H	26	24	23	1.085156	119.755624	179.129947	−2.763638	−3.000593	−1.262274
32	H	28	25	23	1.085192	119.923924	179.128540	−5.666193	−0.961893	1.161550
33	H	30	26	24	1.085406	120.021512	−179.45157	−4.930895	−2.997222	−0.055456

Atom no. + NA = bond; atom no. + NA + NB = angle; atom no. + NA + NB + NC = dihedral; *X*, *Y*, *Z* = Cartesian coordinate

Table 3 Theoretical data of geometry 3D of ibuprofen structure Fig. 7

Atom no.	Atom symbol	NA	NB	NC	Bond/Å	Angle/degree	Dihedral/degree	*X*/Å	*Y*/Å	*Z*/Å
1	C							−5.344193	−0.391737	−0.073699
2	C	1			1.533499			−3.908377	0.028849	0.262692
3	C	2	1		1.532628	110.968339		−3.764188	1.554510	0.239960
4	C	2	1	3	1.548402	110.307879	−124.81127	−2.907268	−0.664465	−0.693679
5	C	4	2	1	1.512320	114.725627	−171.95713	−1.451214	−0.472131	−0.333088
6	C	5	4	2	1.398620	121.722769	−102.95775	−0.635549	0.430073	−1.023635
7	C	5	4	2	1.398558	120.699294	76.583967	−0.875000	−1.191791	0.718592
8	C	7	5	4	1.391615	121.187798	−179.26057	0.459706	−1.011675	1.068892
9	C	8	7	5	1.397775	121.023931	0.181907	1.268187	−0.101346	0.382282
10	C	6	5	4	1.392256	121.448120	179.130870	0.699596	0.615647	−0.675314
11	C	9	8	7	1.526176	119.910153	178.847222	2.721491	0.095131	0.804794
12	C	11	9	8	1.539472	112.672219	−117.49188	3.010876	1.528426	1.286350
13	C	11	9	8	1.522803	110.693120	115.732674	3.668356	−0.346265	−0.303153
14	O	13	11	9	1.203512	125.287549	−100.26678	4.251627	−1.398308	−0.341129
15	O	13	11	9	1.357746	112.645401	79.431199	3.795765	0.584373	−1.283538
16	H	15	13	11	0.969664	106.779754	−178.12626	4.387565	0.206976	−1.952562
17	H	3	2	1	1.092340	111.865864	178.446103	−2.752879	1.871556	0.504428
18	H	3	2	1	1.096025	110.930258	−61.264223	−3.989283	1.954275	−0.755425
19	H	3	2	1	1.093919	111.000319	58.097737	−4.455537	2.024186	0.945722
20	H	1	2	3	1.094202	111.621688	−177.31754	−5.470817	−1.476968	−0.014382
21	H	1	2	3	1.093915	111.279311	−57.041401	−6.062749	0.063895	0.613852
22	H	1	2	3	1.095578	111.138578	62.622269	−5.619236	−0.082094	−1.087979
23	H	2	1	3	1.098155	107.950253	118.076836	−3.684173	−0.316738	1.280654
24	H	4	2	1	1.096201	108.345300	−49.954280	−3.131917	−1.737280	−0.709711
25	H	4	2	1	1.096595	108.701714	64.932002	−3.085410	−0.301080	−1.7128664
26	H	7	5	4	1.086808	119.562220	1.351961	−1.475436	−1.912454	1.267475
27	H	8	7	5	1.086256	119.438206	−179.46190	0.880490	−1.592105	1.884976
28	H	10	6	5	1.084329	119.469885	179.039011	1.307070	1.312029	−1.242586
29	H	6	5	4	1.086415	119.354536	−1.141572	−1.050454	0.995957	−1.853049
30	H	12	11	9	1.092246	109.716752	58.378307	2.359766	1.772697	2.128602
31	H	12	11	9	1.093519	111.119433	177.912204	4.048146	1.631115	1.616971
32	H	12	11	9	1.090214	111.53542	−61.560487	2.835792	2.259027	0.496328
33	H	11	9	8	1.091807	107.619831	2.624258	2.925379	−0.600868	1.620917

Atom no. + NA = bond; atom no. + NA + NB = angle; atom no. + NA + NB + NC = dihedral; *X*, *Y*, *Z* = Cartesian coordinate

Table 4 Theoretical data of geometry 3D of naproxen structure of Fig. 8

Atom no.	Atom symbol	NA	NB	NC	Bond/Å	Angle/degree	Dihedral/degree	*X*/Å	*Y*/Å	*Z*/Å
1	C							3.885859	−0.287614	−0.721310
2	O	1			1.203526			4.200401	−1.100497	−1.551226
3	O	1	2		1.357674	122.068882		4.242504	1.018639	−0.820235
4	H	3	1	2	0.969650	106.814939	1.587511	4.733425	1.113227	−1.651060
5	C	1	2	3	1.523336	125.297508	179.77366	3.062800	−0.577641	0.527294
6	H	5	1	2	1.091690	104.076543	13.040759	3.055578	−1.667306	0.593366
7	C	5	1	2	1.539900	112.133131	130.592455	3.716109	−0.005077	1.798769
8	H	7	5	1	1.090248	111.693070	64.502935	3.760674	1.083967	1.773528
9	H	7	5	1	1.092183	109.688366	−175.472854	3.137868	−0.303553	2.675931
10	H	7	5	1	1.093478	111.043605	−55.989345	4.736049	−0.380432	1.919267
11	C	5	1	2	1.524927	110.860997	−102.409466	1.620639	−0.116315	0.346316
12	C	11	5	1	1.375987	120.150019	114.162746	0.599140	−1.037654	0.314455
13	C	11	5	1	1.423710	121.227711	−66.783075	1.296962	1.264999	0.227337
14	C	12	11	5	1.419271	121.794375	178.518312	−0.757991	−0.645071	0.178796
15	H	12	11	5	1.086960	119.843092	−1.336591	−0.824217	−2.097862	0.396801
16	C	13	11	5	1.370642	121.140078	−178.588597	−0.002623	1.679498	0.093437
17	H	13	11	5	1.083884	119.245784	2.366242	2.095475	1.997925	0.227594
18	C	16	13	11	1.422134	121.198915	−0.027581	−1.074819	0.745578	0.067860
19	C	14	12	11	1.414487	122.539628	−179.753647	−1.820636	−1.578180	0.149342
20	H	16	13	11	1.086127	119.975294	−179.910734	−0.227956	2.738107	0.002636
21	C	18	16	13	1.410786	122.550231	179.818755	−2.422618	1.140707	−0.064913
22	C	19	14	12	1.376047	121.543191	179.901585	−3.129675	−1.174539	0.018970
23	H	19	14	12	1.086147	119.012028	−0.128115	−1.594108	−2.637273	0.231337
24	C	21	18	16	1.381223	120.956302	179.811741	−3.438201	0.204892	−0.089768
25	H	21	18	16	1.084941	120.414935	−0.124104	−2.681211	2.190871	−0.150832
26	H	22	19	14	1.082719	119.374199	179.974470	−3.915616	−1.918998	0.000054
27	O	24	21	18	1.364635	116.399847	−179.977790	−4.706923	0.689720	−0.222108
28	C	27	24	21	1.418565	119.007234	179.852159	−5.792053	−0.223291	−0.257204
29	H	28	27	24	1.088517	105.692470	−179.961158	−6.686765	0.386872	−0.367024
30	H	28	27	24	1.095389	111.713148	−61.427132	−5.718300	−0.907845	−1.109157
31	H	28	27	24	1.095416	111.710380	61.497945	−5.864549	−0.802348	0.669820

Atom no. + NA = bond; atom no. + NA + NB = angle; atom no. + NA + NB + NC = dihedral; *X*, *Y*, *Z* = Cartesian coordinate

The DSC curve of ketoprofen (with heating and cooling) is shown in Fig. 4. In the first heating the fusion is observed (peak at 96 °C); and in the first cooling as well as for the second heating and second cooling no peaks is observed. Purity of 99.3% was calculated according Van't Hoff equation and with $\Delta H = 30.83$ kJ/mol.

TG–DTA curves of ibuprofen Fig. 2b show thermal stability up to 127 °C. The thermal decomposition occurs between 127 and 253 °C with total mass loss corresponding to an endothermic peak at 239 °C. Fusion of this compound begins at 71 °C with peak at 81 °C, in agreement with the literature [13].

X-ray powder patterns of the ibuprofen and ibuprofen recrystallized shows same structure.

DSC curve of ibuprofen Fig. 5 shows in the first heating the melting at 78.5 °C. No peak is observed during the first cooling and the second heating and cooling, however is observed that the ibuprofen returns slowly to solid state after fusion (approximately 1 h). Purity of 98.5% was calculated according Van't Hoff equation with $\Delta H = 31.71$ kJ/mol.

TG–DTA curves of naproxen Fig. 2c show thermal stability up to 165 °C. The first mass loss occurs between 158 and 306 °C ($\Delta m = 99\%$) corresponding to the endothermic peak at 295 °C and the second mass loss occurs between 307 and 450 °C ($\Delta m = 1\%$) corresponding to the exothermic peaks at 322 and 447 °C.

The endothermic peak at 157 °C is due to the fusion of naproxen. Purity by DSC was not calculated because the fusion occurs together with the thermal decomposition.

Infrared spectroscopic data of ketoprofen, ibuprofen, and naproxen (theoretical and experimental) are shown in

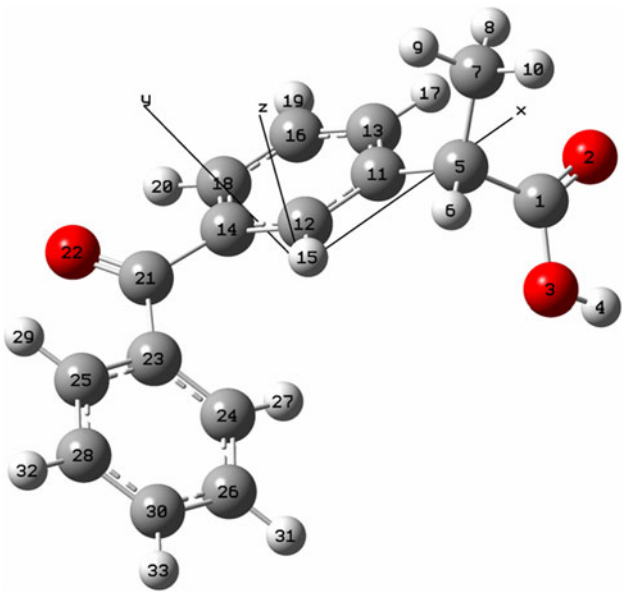

Fig. 6 Theoretical 3D structure of ketoprofen

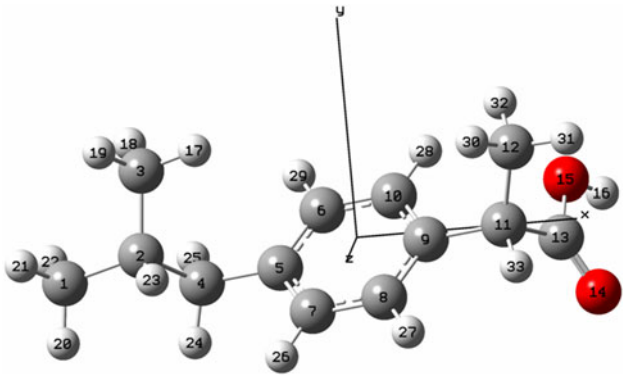

Fig. 7 Theoretical 3D structure of ibuprofen

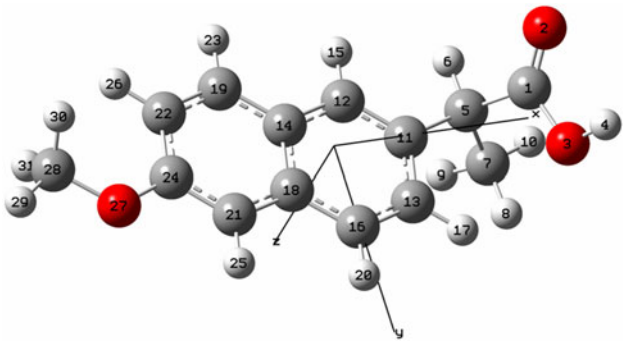

Fig. 8 Theoretical 3D structure of naproxen

Table 1. Theoretical data of ketoprofen, ibuprofen, and naproxen are shown in Tables 2, 3, and 4. The optimized structures of the ketoprofen, ibuprofen, and naproxen are shown in Figs. 6, 7 and 8. The theoretical infrared spectrum helped in the interpretation of experimental infrared and provided information about geometry 3D of the compounds.

Conclusions

TG–DTA curves supplied information on thermal stability and thermal decomposition of the studied compounds. The DSC curves allowed us to determine the melting point of ketoprofen and ibuprofen as well as the enthalpy (ΔH_{fusion}) and purity by using the Van't Hoff equation. The results are in agreement with the manufacturer's specifications. Studies on reversibility processes were realized by DSC with heating and cooling.

Theoretical calculations help in interpretations of FTIR spectra supplying structural. The theoretical results are therefore in agreement with the experimental data.

The reflectance FTIR spectra show the formation of polymeric structure through the carboxyl groups ($-COO^-$) for ketoprofen and ibuprofen. For naproxen was not

possible to verify the modifications, because fusion occurs simultaneously with decomposition.

Acknowledgements The authors thank FAPESP (Proc. 2008/04296; 2006/06951-3), CNPq and CAPES foundation (Brazil) for financial support and computational facilities of CENAPAD-UNICAMP.

References

1. Giordano F, Novak C, Moyano JR. Thermal analysis of cyclodextrins and their inclusion compounds. Thermochim Acta. 2001;380:123–51.
2. Giron D. Thermal-analysis and calorimetric methods in the characterization of polymorphs and solvates. Thermochim Acta. 1995;248:1–59.
3. Valladão DMS, Oliveira LCS, Zuanon Netto J, Ionashiro M. Thermal decomposition of some diuretic agents. J Therm Anal. 1996;46:1291–9.
4. Ribeiro YA, Oliveira JDS, Leles MIG, Juiz AS, Ionashiro M. Thermal decomposition of some analgesic agents. J Therm Anal. 1996;46:1645–55.
5. Wesolowski M. The influence of various tablet components on thermal-decomposition of some pharmaceuticals. Mikrochim Acta. 1980;1:199–213.
6. Neto HS, Novak C, Matos JR. Thermal analysis and compatibility studies of prednicarbate with excipients used in semi solid pharmaceutical form. J Therm Anal Calorim. 2009;97:367–74.
7. Bernardi LS, Oliveira PR, Murakami FS, Silva MAS, Borgmann SHM, Cardoso SG. J Therm Anal Calorim. 2009;97:729–33.
8. Petit S, Mallet F, Petit MN, Coquerel G. Role of structural and macrocrystalline factors in the desolvation behaviour of cortisone acetate solvates. J Therm Anal Calorim. 2007;90:39–47.
9. Lvova MSh, Kozlov EI, Wishnevezkaya IA. Thermal-analysis in the quality-control and standardization of some drugs. J Therm Anal. 1993;40:405–11.
10. Schnitzler E, Carvalho-Filho MAS, Stadler CC, Volpato AM, Ionashiro M. Application of differential scanning calorimetry (DSC) in the thermal characterization of dexamethasone acetate, excipients and dexamethasone cream. Ecl Quím. 2001;26:41–52.
11. Wesolowski M, Szynkaruk P. Thermal decomposition of purine derivatives used in medicine. J Therm Anal Calorim. 2001;65:599–605.
12. Schnitzler E, Kobelnik M, Sotelo GFC, Bannach G, Ionashiro M. Thermoanalytical study of purine derivatives compounds. Ecl Quim. 2004;29:71–8.
13. The Merck Index, Merck & Co. Inc., 11th ed. New York: Rohway; 1989.
14. Giron DJ. Applications of thermal-analysis in the pharmaceutical-industry. J Pharm Biomed Anal. 1986;4(6):755–70.
15. Lerdkanchanaporn S. A thermal analysis study of ibuprofen and starch mixtures using simultaneous TG–DTA. Thermochim Acta. 1999;131:340–1.
16. Giron D, Goldbronn C. Use of DSC and TG for identification and quantification of the dosage form. J Therm Anal. 1997;48:473–83.
17. Royall PG, Craig DQM, Grandy DB. The use of micro-thermal analysis as a means of in situ characterisation of a pharmaceutical tablet coat. Thermochim Acta. 2001;380:165–73.
18. Lerdkanchanaporn S, Dollimore D. A thermal analysis study of ibuprofen. J Therm Anal. 1997;49:879–86.
19. Mura P, Mandersioli A, Bramanti G, Furlanetto S, Pinzauti S. Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients. Int J Pharm. 1995;119:71–9.
20. Mura P, Faucci MT, Manderioli A, Bramanti G, Parrini P. Thermal behavior and dissolution properties of naproxen from binary and ternary solid dispersions. Drug Dev Ind Pharm. 1999;25(3):257–64.
21. Bettinetti G, Bruni G, Giordano F, Mura P. Thermal-analysis of the dehydration process of cross-linked polyvinylpyrrolidone and its mixtures with naproxen. Drug Dev Ind Pharm. 1994;20(14):2215–25.
22. Bettinetti G, Mura P, Giordano F, Setti M. Thermal behaviour and physicochemical properties of naproxen in mixtures with polyvinylpyrrolidone. Thermochim Acta. 1992;199:165–71.
23. Bannach G, Schnitzler E, Treu Filho O, Utuni VHS, Ionashiro M. Synthesis, characterization and thermal studies on solid compounds of 2-chlorobenzylidenepyruvate of heavier trivalent lanthanides and yttrium(III). J Therm Anal Calorim. 2006;83:233–40.
24. Becke AD. Density-functional thermochemistry. 3. The role of exact exchange. J Chem Phys. 1993;98:5648–52.
25. Lee C, Yang W, Parr RG. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron-density. Phys Rev B. 1988;37:785–9.
26. Mclean AD, Chandler GS. Contracted gaussian-basis sets for molecular calculations. 1. 2nd row atoms, z = 11–18. J Chem Phys. 1980;72:5639–48.
27. Krishnan R, Binkley JS, Seeger R, Pople JA. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. J Chem Phys. 1980;72:650–5.
28. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Rega N, Salvador P, Dannenberg JJ, Malick DK, Rabuck AD, Raghavachari K, Foresman, J B, Cioslowski J, Ortiz JV, Baboul AG, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA. Gaussian 03, Revision B.04. Pittsburgh, PA: Gaussian, Inc.; 2003.
29. Schelegel HB. In: Bertran J, editor. New theoretical concepts for understanding organic reactions. The Netherlands: Academic; 1989. pp. 33–53.
30. Goodson DZ, Sarpal SK, Wolfsberg M. Influence on isotope effect calculations of the method of obtaining force constants from vibrational data. J Phys Chem. 1982;86:659–63.
31. Dennington R II, Keith T, Millam J, Eppinnett K, Lee Hovell W, Gilliland R. Gaussview, version 3.0. Shawnee Mission, KS: Semichem, Inc.; 2003.