Effects of Experimental Conditions on the Thermal Behaviour of Some Non-steroidal Anti-inflammatory Drugs

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Data on the thermal stability of drugs was required to obtain information for handling, storage, shelf life and usage. In this work, the thermal stability of four non-steroidal anti-inflammatory drugs (NSAIDs): Ibuprofen (IB), Ketoprofen (KT), Indomethacin (IND) and Piroxicam (PX) was determined by simultaneous thermogravimetery/differential thermal analysis (TG/DTG/DTA) techniques. The results of TG/DTG analysis show that the main thermal degradation for IB, KT, IND and PX occurs in the temperature ranges of 175–300°C ; 235–400°C ; 235–450°C respectively 200–450°C. The TG/DTA analysis of compounds mentioned show the following temperatures of melting: IB–78.5°C; KT–96.8°C; IND–162.7°C; respectively PX–200.3°C. Moreover, the influence of heating rate and sample size on the thermal decomposition of examined compounds was evaluated. The results show that the increase of two parameters has influence on the temperature range and the shape of thermoanalytical curves, especially the heating rate.

Keywords: thermal behaviour, ibuprofen, ketoprofen, indomethacin, piroxicam, NSAIDs, TG/DTG/DTA

Non-steroidal anti-inflammatory drugs, NSAIDs, from the carboxylic family, derivatives of N-phenyl anthranilic acid, such as Ibuprofen (IB), Ketoprofen (KT), Indomethacin (IND), and from oxicam family, piroxicam (PX), are widely used in inflammatory and painful disease of rheumatic and non-rheumatic origin. figure 1 shows chemical structure of these drugs.

The anti-inflammatory activity of NSAIDs and most of their other pharmacological effects are related to the inhibition of the conversion of arachidonic acid to prostaglandins, which are mediators of the inflammatory process [1,2].

NSAIDs are potent inhibitors of cyclo-oxigenase in vitro and in vivo, thereby decreasing the synthesis of prostaglandins, prostacyclin and tromboxane products.

Recently, two different cyclo-oxygenase isoforms have been characterised Cox-1 and Cox-2. Inhibition of the Cox-2 enzyme system results in anti-inflammatory action, while inhibition of the Cox-1 enzyme system results in antiinflammatory action as well as gastric irritation [4].

New studies from the last years revealed that in addition to arthritis and pain, cancer and neurodegenerative diseases like Alzheimer's disease could be potentially treated with Cox-2 inhibitors [5,6].

Research in thermal decomposition of drugs is of great interest in developing new product since it is often necessary to predict degradation rates at marketing temperatures from data collected on accelerated processes studied at elevated temperatures.

In pharmaceutical sciences thermal methods of analysis are widely used in the study of stability and thermal decomposition of substances used in medicine [7-15].

The thermal stability is a very important problem, because determining the temperature range when a certain medicine substance is stable regarding its structure as well its pharmaceutical action is crucial for the stocking of the drug, for its technological transformations and for the obtaining technology of right formulas.

The evaluation of drug stability in the solid state is mostly made by analyzing their decomposition under isothermal

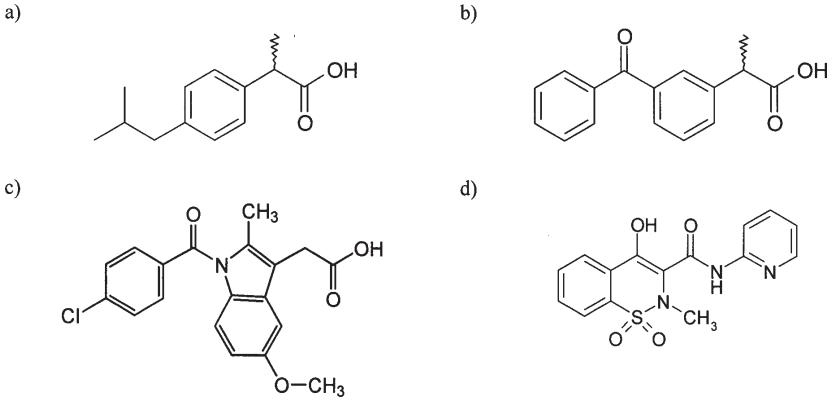

Fig. 1. Chemical structure of:
a) Ibuprofen [2-methyl-4(2-methylpropyl)benzenacetic acid]
b) Ketoprofen (3-benzoyl-α-methylbenzeneacetic acid) c) Indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1Hindole-3-acetic acid]
d) Piroxicam [4-hydroxy-2-methyl-N-(pyridine-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide]

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or non-isothermal conditions. Usually, it proceeds along with mass loss in an irreversible way.

The decomposition reactions of drugs possess both practical and scientific significance. These reactions make possible to know the behaviour of a drug substance at various temperatures, and that knowledge is important for the prediction of storage conditions for drug formulations. They also enable to get information on temperatures, at which the drug substance can be subject to technological processes without loss of its specific physico-chemical and pharmacological properties. The decomposition reactions are also carried out in order to obtain the solid products, which are characterised by proper phase composition and activity for further technological applications.

Also, kinetic parameters obtained from thermoanalytical data are highly useful for making predictions of performance parameters of drugs, for example, "shelf life". One main purpose of kinetic analysis of solid decomposition is to determine reaction mechanism(s) and to calculate Arrhenius parameters, using either isothermal or non-isothermal conditions.

As with any instrumental technique, there is a large number of factors that can affect the nature, precision, and accuracy of thermal experimental result, especially TG result. Because of the dynamic nature of the temperature change of the sample a larger number of variables can affect TG measurements. Basically, the factors that can influence the mass-change curve of a sample fall into two categories: instrumental (furnace heating rate, furnace atmosphere, sample container composition, sample holder geometry and furnace environment) and sample characteristics (sample amount, particle size, thermal conductivity, sample packing and heat of reaction) [7-10;16].

It has often been reported in the literature that the values of the kinetic parameters of thermal decomposition depend on experimental conditions. Many papers illustrate this problem and show the influence, especially of heating rate, sample mass and furnace atmosphere [17-20].

In literature, there are many examples treated with the application of thermal methods of analysis, especially differential scanning calorimetry (DSC), DTA, TG and DTG, in the studies of thermal stability and decomposition of pharmaceuticals [7-15;21-27].

In our previous works [28-37] we provided the importance of the thermal analysis in estimation of thermal stability for different pharmaceuticals, by thermal behaviour and kinetic analysis, respectively their compatibility.

In this work, the IB, KT, IND and PX drugs were investigated by means of TG/DTG/DTA techniques. The results allowed us to acquire information concerning these compounds in the solid state, including their thermal stability and thermal decomposition. Also, the influence of heating rate and sample size on the thermal decomposition of the examined compounds was evaluated.

Experimental part

Materials and methods

The four active substances (AS) are available as pure compounds, able to be used for medicinal purpose. These are obtained from:

- IB – Basf Aktiengesellschaft, Germany, lot: IB1P0741
- KT – S.I.M.S., Italy, lot: 138315
- IND – Euro OTC Pharma Gmb.H., Bonn, Germany, lot:700111 Ch.B
- PX – Nantong Jinghna Pharmaceutical Co. LTD, Chine, lot: PRX2006001

TG/DTG/DTA experiments were performed with a Netzsch-STA 449 TG/DTA instrument in the temperature range of 20 – 500 °C, using platinum crucibles with 10, 25, 50, 75 and 100 mg of samples, under dynamic nitrogen atmosphere (20 mL . min^{-1}) and the heating rates of 2.5, 5, 7.5, 10, 15 and 20 °C . min^{-1}.

Results and discussions

Thermal behaviour

The thermoanalytical curves of IB, KT, IND and PX are presented in figures 2–5, for an experiment carried out at 10 °C . min^{-1} with a sample size of 25 mg in nitrogen.

The TG/DTG curves (fig. 2) show that IB is stable up to 175 °C and presents a single stage of mass loss between 175 and 300 °C (Δm = 98%) and DTG_{peak} = 282.2 °C.

The DTA curve has shown a sharp endothermic peak (T_{peak} = 78.5 °C; T_{onset} = 72.4 °C; ΔH_{fus} = - 448J . g^{-1}) corresponding to the melting point, followed by other endothermic peak due to decomposition (T_{peak} = 271.0 °C).

The melting point obtained from DTA curve is similar to the values mentioned in the speciality literature (76–79 °C) [38,39]. This indicates a high purity of ibuprofen drug.

The DTA curve of KT active substance (fig. 3) shows an endothermic sharp event between 89.4 and 128.6 °C indicating the melting (T_{peak} = 96.8 °C), which corresponds

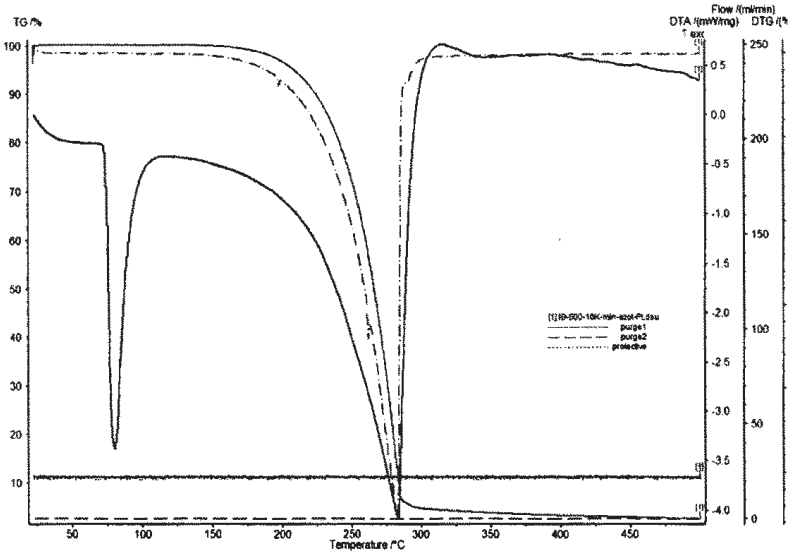

Fig. 2. TG/DTG and DTA curves of IB – AS

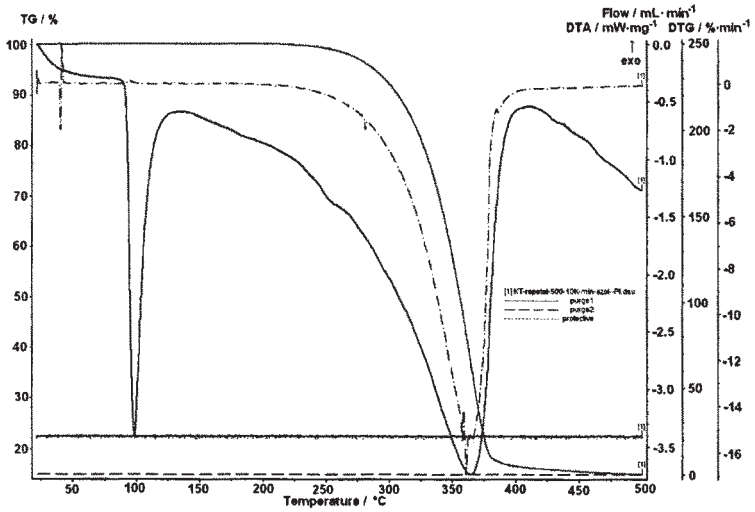

Fig. 3. TG/DTG and DTA curves of KT – AS

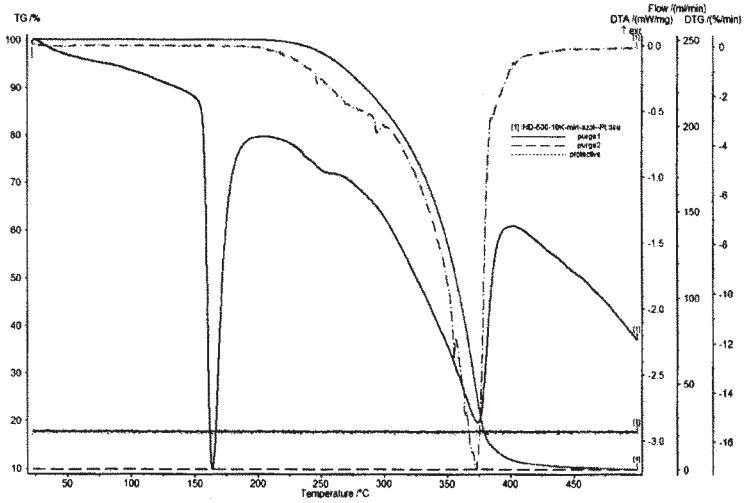

Fig. 4. TG/DTG and DTA curves of IND – AS

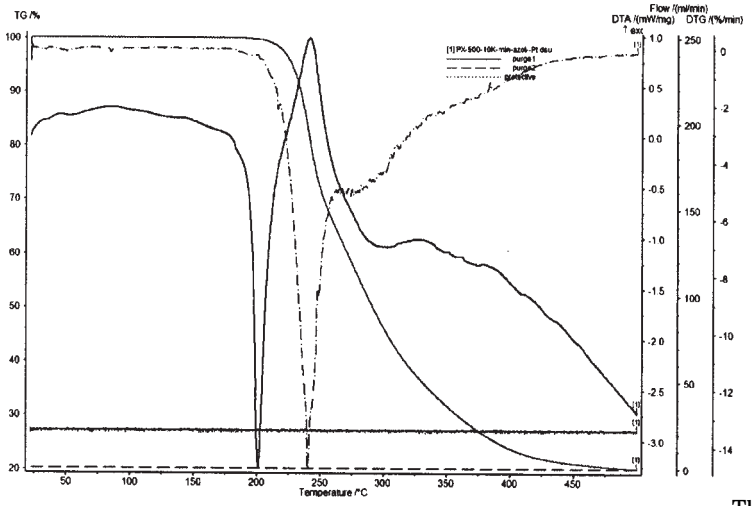

Fig. 5. TG/DTG and DTA curves of PX – AS

to the values indicated in the literature (94–97 °C). In this temperature range the TG/DTG curves did not show mass loss.

The second broad event, observed in DTA curve was also an endothermic one which corresponds to the thermal decomposition process. This is confirmed by TG/DTG curves that indicate thermal decomposition in the following temperature range and mass loss: 235–400°C (Δm = 86%). For the decomposition process the thermal curves indicate the following temperatures of the peaks: DTG_{peak} = 361.4 °C; DTA_{peak} = 365.0°C. The DTA data combined with TG allow evidencing a thermal stability of ketoprofen active substance up to 235 °C.

Also, the DTA curve confirms the purity of ketoprofen AS by a sharp endothermic peak 96.8°C that corresponds to melting followed by thermal decomposition.

Thermal decomposition of the indomethacin drug (fig. 4) takes place in one stage. Thus, the IND –AS decomposes through a unitary process in a temperature range of 235–450°C, with DTG_{peak} = 373.0°C and Δm = 90%.

According to the DTA curve, there can be distinguished two endothermic peaks, very well defined. The first, with the $T_{fus} = T_{DTA\,peak}$ = 162.7°C, corresponds to the melting process, and the melting temperature is similar to the values mentioned in speciality literature (159–163°C). The nature of the peak, sharp and very well defined, together with the value of T_{fus} indicates a high purity of the IND – AS.

After melting, it takes place the decomposition process, with a broad endothermic peak, and DTA_{peak} = 375.0°C.

According to the TG/DTG curves (fig. 5), it can be said that the thermal decomposition of piroxicam active substance occurs in one stage, but through a complex

	β (°C·min^{-1})						m (mg)				
	2,5	5	7,5	10	15	20	10	25	50	75	100
$T_{on\ set}$ (°C)	131	138	150	175	180	200	160	175	200	205	207
$T_{end\ set}$ (°C)	315	320	325	350	360	370	325	350	350	360	367
$T_{DTG\ peak}$ (°C)	250	255	268	282	295	302	262	282	301	316	319
T_t (°C)	70	72	75	79	84	90	75	80	84	89	92

Table 1
RESULTS OF THE THERMAL DECOMPOSITION OF IBUPROFEN FOR DIFFERENT β AND m

	β (°C·min^{-1})						m (mg)				
	2,5	5	7,5	10	15	20	10	25	50	75	100
$T_{on\ set}$ (°C)	220	230	240	250	250	250	200	248	252	257	260
$T_{end\ set}$ (°C)	400	430	465	490	500	500	470	490	500	505	508
$T_{DTG\ peak}$ (°C)	352	355	358	361	369	375	326	361	380	387	392
T_t (°C)	96	96	97	97	99	100	97	98	100	101	102

Table 2
RESULTS OF THE THERMAL DECOMPOSITION OF KETOPROFEN FOR DIFFERENT β AND m

	β (°C·min^{-1})						m (mg)				
	2,5	5	7,5	10	15	20	10	25	50	75	100
$T_{on\ set}$ (°C)	200	210	225	240	250	250	225	240	248	250	250
$T_{end\ set}$ (°C)	400	405	415	430	440	445	425	430	450	455	470
$T_{DTG\ peak}$ (°C)	325	348	355	373	375	384	345	375	387	390	394
T_t (°C)	160	162	162	163	166	170	160	164	166	170	174

Table 3
RESULTS OF THE THERMAL DECOMPOSITION OF INDOMETHACIN FOR DIFFERENt β AND m

	β (°C·min^{-1})						m (mg)				
	2,5	5	7,5	10	15	20	10	25	50	75	100
$T_{on\ set}$ (°C)	200	204	210	220	225	228	210	220	225	229	232
$T_{end\ set}$ (°C)	450	450	450	450	450	450	450	450	450	450	450
$T_{DTG\ peak}$ (°C)	230	235	245	240	255	260	235	240	248	249	251
T_t (°C)	200	200	200	200	205	205	200	202	209	212	213

Table 4
RESULTS OF THE THERMAL DECOMPOSITION OF PIROXICAM FOR DIFFERENT β AND m

process, especially after a mass loss of about 30–35 %, with successive and/or simultaneous reactions. The corresponding decomposition temperature range is between 200 and 450 °C with a mass loss of about 80% and DTG_{peak} = 240.2°C. Over 450°C, the TG/DTG curves indicate a light and permanent mass loss, caused by the formation of carbon in the decomposition stage, as a result of the breaching aromatic rings.

The DTA curve shows a sharp first peak, of endothermic nature, at 200.3°C which indicates the melting process, and which corresponds to the values mentioned in speciality literature (197–201°C). The nature of the peak, sharp and very well defined, together with the value of T_{fus}, indicates a high purity of the PX – AS. Once the melting takes place, the decomposition also begins in the mentioned temperature range. The decomposition process has an exothermic nature (DTA_{peak} = 243.5°C) which is under-standable considering the presence of sulphur in the piroxicam's molecule with oxygen.

Effect of heating rate and sample size

In order to evaluate the effect of changing the experimental variables on the thermal decomposition, the experiments were carried out with different heating rates and sample sizes. Tables 1–4 summarize some general characteristic for the curves recorded: with the m = 25 mg for the heating rates (β) of 2.5, 5, 7.5, 10, 15 and 20 °C×min^{-1}, respectively β = 10 °C . min^{-1} for the sample sizes (m) of 10, 25, 50, 75 and 100 mg.

Based on the analysis of DTA, TG and DTG curves of the examined compounds, recorded as a result of a heating rate increase, it was concluded, that the heating rate has significant influence on the temperature range and the shape of thermoanalytical curves. Along with the increase of heating rate, the temperature ranges, at which the endothermic effect and the peak temperature occurred, become shifted into the higher values. On the other hand, the curves recorded as a function of temperature, peaks become higher and wider, whereas TG curves become flatter. When curves are recorded as a function of time, DTA and DTG peaks become narrower and the TG curve becomes steeper. Above changes are due to the increase of the degree of reactivity of compound in a short period of time and the temperature interval between surface and interior grows up together with increase of heating rate.

By analysing the influence of a sample size on the results of the thermal decomposition of anti-inflammatory compounds, one can conclude, that along with the increase of the sample size at the same heating rate, proceeds change in the shape of DTA and DTG curves. The height of peaks and their area enlarge proportionally to the heat value being exchanged by a sample with the environment of the temperature of the peak and their ends towards higher values were observed.

Conclusions

The thermal stability of the four drug samples was determined by simultaneous thermogravimetry/derivative thermogravimetry/differential thermal analysis (TG/DTG/DTA). Also, the influence of heating rate and sample size on the thermal decomposition of anti-inflammatory derivatives was evaluated.

According to the TG/DTA data, it was verified that the thermal decomposition of ibuprofen, ketoprofen and indomethacin started after their melting points. In the case of piroxicam, the thermal decomposition occurs practically with the melting.

The four non-steroidal anti-inflammatory drugs: ibuprofen, ketoprofen, indomethacin and piroxicam decompose via a single stage process in an atmosphere of nitrogen.

Results of the studies showed that thermoanalytical methods can be useful to determine the temperature ranges corresponding to the thermal stability of compounds. This is a very important problem because the determination of the temperature range, in which a given drug substance is stable both in its structure and pharmacotherapeutic action, is crucial from the point of view of drug storage, its technological transformation and technology of drug formulations.

A considerable effect of heating rate and sample size on the thermal decomposition of anti-inflammatory derivatives may be due to a complexity of the thermal rearrangement of examined compounds to the intermediate products.

The procedural variables can affect the shape of the DTA curves. An increase in the heating rate causes an

increase in the peak temperature, and an increase in the peak.

An increase in sample size causes an increase in the reaction temperature.

It can be concluded that the heating rate influences the thermal decomposition of the analyzed compounds at a higher extent than sample size.

References

1. TESLYUK O, BEL'TYUKOVA S, YEGOROVA A, YAGODKIN B. Complex compounds of terbium(III) with some nonsteroidal anti-inflammatory drugs and their analytical applications. J Anal Chem., **62**, 2007, p. 330.
2. KOVALA-DEMERTZI D. Transition metal complexes of diclofenac with potentially interesting anti-inflammatory activity. J Inorg Biochem. **79**, 2000, p. 153.
3. KOVALA-DEMERTZI D. Recent advances on non-steroidal antiinflammatory drugs, NSAIDs: Organotin complexes of NSAIDs. J Organomet Chem. **691**, 2006, p. 1767.
4. GALICO DA, HOLANDA BB, PERPETUO GL, SCHNITZLER E, TREUFILHO O, BANNACH G. Thermal and spectroscopic studies on solid Ketoprofen of lighter trivalent lanthanides. J Therm Anal Calorim. **108**, 2012, p. 371.
5. CHATTERJEE NR, KULKARNI AA, GHULEKAR SP. Synthesis, pharmacological activity and hydrolytic behavior of ethylenediamine and benzathine conjugates of ibuprofen. Eur J Med Chem. **43**, 2008, p. 2819.
6. KOBELNIK M, RIBEIRO CA, DOS SANTOS DIAS D, ALMEIDA S, CRESPI MS, CAPELA JMV. Study of the thermal behavior of the transition phase of Co(II)–diclofenac compound by non-isothermal method. J Therm Anal Calorim. **105**, 2011, p. 467.
7. WESOLOWSKI M, SZYNKARUK P. Thermal decomposition of purine derivatives used in medicine. J Therm Anal Calorim. **65**, 2001, p. 599.
8. BASU P, ALEXANDER SK, RIGA TA. A statistical model for the optimization of DSC performance in the evaluation of drugs for preformulation studies. J Therm Anal Calorim. **83**, 2006, p. 19.
9. ARAGAO SFC, FILHO BMJ, MACEDO OR. Thermal characterization of warifteine by means of TG and a DSC photovisual system. J Therm Anal Calorim. **64**, 2001, p. 185.
10. MURAKAMI SF, LANG LK, CRUZ PA, SILVA SAM. Physico-chemical solid-state characterization of omeprazole sodium: Thermal, spectroscopic and crystallinity studies. J Pharm Biomed Anal. **49**, 2009, p. 72.
11. CARVALHO OT, MATIAS BEA, BRAGA RL, PRADO SGA. Calorimetric studies of removal of nonsteroidal anti-inflammatory drugs diclofenac and dipyrone from water. J Therm Anal Calorim. **106**, 2011, p. 475.
12. ZAYED AM, HAWASH FM, FAHMEY AM, EL-GIZOULI MMA. Investigation of ibuprofen drug using mass spectrometry, thermal analyses, and semi-empirical molecular orbital calculation. J Therm Anal Calorim. **108**, 2012, p. 315.
13. LUST A, LAIDMAL I, PALO M, MEAS A, AALTONEN J, VESKI P. Solid-state dependent dissolution and oral bioavailability of piroxicam in rats. Eur J Pharm Sci. **48**, 2013, p. 47.
14. MOCANU M.A, MOLDOVEANU C, ODOCHIAN L, PAIUS M.C, APOSTOLESCU N, NECULAU R. Study on the thermal behaviour of casein under nitrogen and air athmosphere by means of the TG-FTIR tehnique. Thermochim Acta. **546**, 2012, p. 120.
15. KHANMOHAMMADI M, SOLEIMANI M, MOROVVAT F, GARMARUDI B.A, KHALAFBEIGI M, GHASEMI K. Simoultaneous determination of paracetamol and codeine phosphate in tablets by TGA and chemometrics. Thermochim Acta. **530**, 2012, p. 128.
16. LIU Y, ZHAO J, ZHANG H, ZHU Y, WANG Z. Thermal decomposition of basic zinc carbonate in nitrogen atmosphere. Thermochim Acta. **414**, 2004, p. 121.
17. SOVIZI RM. Thermal behaviour of drugs. Investigation on decomposition kinetic of naproxen and celecoxib. J Therm Anal Calorim. **102**, 2010, p. 285.
18. ARANJO SAA, CIDES SCL, MATOS RJ, BRUNS ER. Effects of experimental conditions on the estimation of kinetic parameters of the thermal decomposition of AZT using factorial design. J Therm Anal Calorim. **79**, 2005, p. 697.
19. BIGDA R, MIANOWSKI A. Influence of heating rate on kinetic quantities of solid phase thermal decomposition. J Therm Anal Calorim. **84**, 2006, p. 453.
20. IVASHCHENKO VA, YAMANUSHKIN MP, MITKIN DO, LENEVA AI, FEDYAKINA TI. Synthesis and antiviral activity of functionally substituted indole-3-acetic acids. Pharm Chem J. **45**, 2011, p. 261.
21. BOICO NB, KOLPAKOV MI. DSC monitoring of piracetam concentration stability during experimental storage. Pharm Chem J. **45**, 2011, p. 309.
22. FINDORAKOVA L, SVOBODA R. Kinetic analysis of the thermal decomposition of Zn(II) 2-chlorobenzoate complex with caffeine. Thermochim Acta. **543**, 2012, p. 113.
23. BAKHBAKHI Y, ALFADUL S, AJBAR A. Precipitation of ibuprofen sodium using compressed carbon dioxide as antisolvent. Eur J Pharm Sci. **48**, 2013, p. 30.
24. ZHONG BO, CAI X, YI X, LIU L, PINK JJ, XU Y, SU B. From COX-2 inhibitor nimesulide to potent anti-cancer agent: Syntesis, *in vitro, in vivo* and pharmacokinetic evaluation. Eur J Med Chem. **47**, 2012, p. 432.
25. REDASANI KV, BARI BS. Synthesis and evaluation of mutual prodrugs of ibuprofen with menthol, thymol and eugenol. Eur J Med Chem. **56**, 2012, p. 134.
26. TSILIOU S, KEFALO A-L, TUREL I, PSOMAS G. Cobalt (II) complexes with non-steroidal anti-inflammatory drug tolfenamic acid: Structure and biological evaluation. Eur J Med Chem. **48**, 2012, p. 134.
27. WESOLOWSKI M, SZYNKARUK P, MAKURAT E. DSC and IR as supporting tools for identification of methylxanthines in solid dosage forms of drugs. J Thermal Anal Calorim. **109**, 2012, p. 807.
28. TITA ,D, TITA, B. Thermal stability of Ketoprofen. Kinetic study of the active substance under isothermal conditions. J Therm Anal Calorim. **111**, 2013, p. 1979.
29. TITA, B, JURCA T, TITA, D. Thermal stability of pentoxifylline: active substance and tablets. Part 1. Kinetic study of the active substance under non-isothermal conditions. J Therm Anal Calorim. **113**, 2013, p. 291.
30. MARIAN E, TITA, B, JURCA T, VICA' L, TITA, D. Thermal behaviour of erythromycin – active substance and tablets. Part. 1. Kinetic study of the active substance under non-isothermal conditions. J Therm Anal Calorim. **111**, 2013, p. 1025.
31. MARIAN E, TITA, B, VICAS, L, JURCA T, TITA, D. Thermal behaviour of active substance versus pharmaceutical compounds from Erythromycin. Rev Chim (Bucharest). **63**, 2010, p. 996.
32. TITA, D, TITA, B. Thermal stability of ketoprofen – active substance and tablets. Part 1. Kinetic study of the active substance under non-isothermal conditions. J Therm Anal Calorim. **105**, 2011, p. 501.
33. TITA, B, BANDUR G, MARIAN E, TITA, D. Compatibility study between ketoprofen and pharmaceutical excipients used in solid dosage forms. J Pharm Biomed Anal. **56**, 2011, p. 221.
34. TITA, B, SZABADAI Z, RUSU G, BANDUR G, TITA, D. Compatibility study between ibuprofen and excipients in their physical mixtures. J Therm Anal Calorim. **105**, 2011, p. 517.
35. TITA, B, BANDUR G, RUSU G, TITA ,D. Thermal stability of ibuprofen. Kinetic study under non-isothermal conditions. Rev Roum Chim. **55**, 2010, p. 553.
36. TITA, B, STEFANESCU M, TITA, D. Complexes of the anti-inflammatory non-steroidal drugs from oxicam family. 1. Synthesis and characterization of the Zn(II) complex with piroxicam. Rev Chim (Bucharest). **62**, 2011, p. 1002.
37. TITA, B, STEFANESCU M, TITA, D. Complexes of the anti-inflammatory non-steroidal drugs from carboxylic acid family. 1. Synthesis and characterization of the Zn(II) complex with ibuprofen. Rev Chim (Bucharest). **62**, 2011, p. 1060.
38. *** Farmacopeea Română, Ed. a X-a, Editura Medicală, Bucureşti, 1993.
39. *** Farmacopeea Europeană, Ed. a 6-a, Council of Europe, Strasbourg, 2007

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