The application of thermal methods is of great importance in the solution of pharmaceutical problems, such as the control of raw materials, the determination of purity, the qualitative and quantitative analysis of drug formulation, tests of thermal stability and compatibility, the determination of kinetic parameters etc. The evaluation of thermal stability in the solid state is mostly made by analyzing their decomposition under isothermal and non-isothermal conditions. In this study, simultaneous thermogravimetry/derivative thermogravimetry (TG/DTG) and differential thermal analysis (DTA) were used for characterization of the thermal behaviour of ibuprofen (IB) – active substance (AS) under dynamic nitrogen atmosphere and non-isothermal conditions, in comparison with pharmaceutical product (IB–M) containing the corresponding active substance. It was observed that the commercial samples showed a different thermal profile than the standard sample, caused by the presence of excipients in the molecule and to possible interaction of these with the active substance. These excipients decrease the thermal stability of the pharmaceutical products. The Fourier transformed infrared spectroscopy (FT-IR) and X-ray powder diffraction (XRPD) were used as complementary techniques adequately implement and assist in interpretation of the thermal results. The main conclusion of this comparative study was that the TG/DTG and DTA diagrams, together with the FT-IR spectra, respectively X-ray diffractograms constitute believe data for the discrimination between the pure substance and pharmaceutical forms.

Keywords: ibuprofen, active substance, pharmaceutical product, TG/DTG/DTA, FT-IR, X-ray

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of rheumatism diseases, as rheumatoid arthritis, and pain. The pharmacological effects of NSAIDs are due to inhibition of a membrane enzyme called cyclo-oxygenase (Cox) which is involved in the prostaglandin biosynthesis. The discovery in 1990 of two isoforms, Cox-1 and Cox-2, helped to understand the side-effects of NSAIDs. The constitutive Cox-1 is found in healthy populations and has mainly a physiological role in kidneys and the stomach. In contrast, the mainly inducible Cox-2 involved in the production of prostaglandins mediating pain and supporting the inflammatory process [1-3].

Classical NSAIDs such as aspirin and ibuprofen non-selectively inhibit both isoenzymes and cause gastric failure. Gastrointestinal (GI) side effects constitute the most frequent of all the adverse reactions of NSAIDs. Even though ibuprofen (fig. 1) is very potent and widely used among other clinically used NSAIDs, literature is abundant with its gastric and other side effects because of the presence of free carboxylic group. These reactions range in both severity and frequency leading to GI bleeding, ulceration and haemorrhage. The major factor in the development of GI ulceration and haemorrhage induced by NSAIDs is the inhibition of prostaglandins synthesis, as the endogenous prostaglandins are known to have cytoprotective action on the gastric mucosa. In order to prevent or decrease these side-effects, a current strategy consists of designing selective Cox-2 inhibitors as NSAIDs with an improved gastric safety profile [4-6].

Thermal analysis is one of the most frequently used instrumental techniques in the pharmaceutical research, for the thermal characterization of different materials from solid to semi-solids, which are of pharmaceutical relevance. The term “thermal characterization” refers to the thermal stability and decomposition of the substances used in medicine.

The application of thermal methods, especially TG, DTG and DTA or differential scanning calorimetry (DSC) is very important when solving pharmaceutical problems, like for example the determination of purity level, qualitative and quantitative analysis of the medicinal compositions, stability tests, kinetic parameters determination [7-14].

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 as its pharmaceutical action is crucial for the stocking of the drug, for its technological transformations and for the obtaining technology of the right formulas.

The evaluation of the stability of a drug in solid form is realized especially by analyzing its decomposition in isothermal and non-isothermal conditions. Usually, this takes place by irreversible weight loss. The drugs decomposition reactions have a theoretical, as well as a practical signification. Research in thermal decomposition of drugs is of great interest in developing new products since it is often necessary to predict degradation rates at marketing temperatures from collected data on accelerated processes studied at elevated temperatures.
Thermogravimetry is an analytical, quantitative and comparative method, capable of producing fast and reproducible results. It can be used in the quality control of drugs, with a view to the improvement of the final product and for the determination of drug quality via technological parameters.

Thermogravimetry, during which the change of mass of a sample heated at constant rate is recorded and plotted versus temperature, is an effective method of studying thermal stability and for determining the kinetic parameters of the decomposition of drugs and medicines [15-19].

Differential scanning calorimetry, which is frequently used instead of the DTA, can be used in pharmaceutical research as an analytical tool of great importance for the identification and purity testing of active drugs and especially to elucidate the miscibility/incompatibility with its effects on thermal stability, yielding results rapidly and efficiently [20-26].

In our previous articles we provided the importance and utility of the thermal analysis in estimation of thermal stability and compatibility of different pharmaceuticals by the thermal behaviour, respectively kinetic analysis [27-36].

The purpose of this article is to evaluate the thermal behaviour of ibuprofen active substance, in comparison with pharmaceutical products, together with the finding of the melting point through DTA, which is a criterion for the quality control.

As pharmaceutical products were studied three from the main used commercial products (drugs).

Also, the FT-IR spectra and X-ray diffractograms of pure substance and the pharmaceuticals were drawn up in order to establish an easy way for sample identification by means of a simultaneous analysis of TG/DTG and DTA curves, respectively FT-IR spectra and X-ray diffractograms.

The influence of heating rate on the thermal decomposition was followed through DTA.

Experimental part

Materials and methods

The substances examined by thermal analysis, FT-IR spectroscopy and X-ray analysis were:
- ibuprofen – active substance (IB–AS)
- ibuprofen – capsules (Paduden) (IBPAD) or drug
- ibuprofen – filmed tablets (Rupan) (IBRP) or drug
- ibuprofen – filmed tablets (Ibuprofen-Cipla) (IBCIPLA) or drug

The active substance was obtained from BASF Aktiengesellschaft, Germany, lot: IB1P0741, as pure compound, able to be used for medical purposes.

The pharmaceutical (drugs) were commercial products, containing different excipients like:
- IBPAD: lactose monohydrate, starch, povidone K30, colloidal silicon dioxide, talc, magnesium stearate;
- IBRP: microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, magnesium stearate, croscarmelose sodique;
- IBCIPLA: starch, lactose, methylcellulose, magnesium stearate, colloidal silicon dioxide, amidoglicolate of sodium.

Thermal analysis

The TG/DTG and DTA curves were recorded using a Netzsch-STA 449 TG/DTA instrument in the temperature range 20–500 °C, under a dynamic atmosphere of nitrogen (20 mL . min⁻¹) and at a heating rate (β) of 2.5; 5; 7.5; 10; 15 and 20°C . min⁻¹, using platinum crucibles and weighed approximately 20 mg of samples.

Fourier transformed infrared spectroscopy (FT-IR) and X-ray diffraction

FT-IR spectra were recorded on a Perkin-Elmer Model 1600 apparatus using KBr discs in the range 4000–400 cm⁻¹.

X-ray diffraction patterns (XRPD) were obtained with a Bruker D8 Advance X-ray diffractometer using MoKα radiation (Zr filter on the diffracted beam, 50 kV and 40 mA) in a Bragg–Brentano 0:2θ configuration, with Soller and fixed slits and a NaI (Tl) scintillation detector. The measurements of 2θ ranged between 0° and 30°. Data analysis and acquisition were performed using DIFFRACTplus software from Bruker AXS.

Results and discussions

Thermal behaviour

The thermoanalytical curves for the studied samples are presented in figures 2–5 and these correspond for β = 10 °C . min⁻¹ and m = 20 mg.

The main observations are summarized in table 1.

From the thermal curves and thermoanalytical date (table 1) it is observed that the IB–AS presents a thermal stability relatively reduced, and, at 78.5°C (T onset = 75.0°C; T endset = 92.1°C), this substance is melting.
The melting process is followed by decomposition, which takes place in one step, with a single well defined process. The loss of mass is practically complete ($\Delta m = 98\%$).

The melting points obtained from the DTA curves are similar to the values mentioned in speciality literature 76–79°C [37,38]. These values together with the accuracy of the melting peaks indicate a high purity of ibuprofen.
Melting and decomposition processes are accompanied by endothermic effects. Just as expected, the pharmaceutical (commercial) products show supplementary decomposition steps in comparison to the active substance. These steps are accentuated on the DTG and DTA curves, by the corresponding peaks and are due to the presence of excipients, in fact to their possible interactions with the active substance.

For example:
- the microcrystalline cellulose, as methylcellulose, lost the absorbed water below 110°C, between 35 and 110°C, apparently in a single endothermic process;
- the lactose monohydrate (α-lactose) lost the water content between 100 and 170°C;
- for povidone K30, apparently, dehydration is completed at 110 °C in N2. However, a second loss stage begins past 150 °C and completes around 250°C;
- the magnesium stearate lost the surface and structural water in several stages, below 110°C.

According to the thermoanalytical curves, the active substance, as well as the pharmaceutical products acts in the same manner thermally, but still showing some differences regarding the nature and the number of the processes taking place, which was expected.

The differences which appear between the thermoanalytical curves of the three pharmaceuticals are due to the different composition as regards the excipients from molecule.

By comparison of thermal curves, it is found that IB–AS has a better thermal stability than pharmaceutical correspondant: IBPAD, IBRP and IBCIPLA, because of the reasons already mentioned.

A practical example for the influence of the heating rate is the variation mode of the melting point, its values being determined from DTA curves and included in table 2.

It is evident that an increase in the heating rate causes an increase in the fusion temperature, and an increase in the peak height.

Also, the TG/DTG and DTA curves shifted to higher temperatures with increasing heating rate.

**Spectroscopy FT-IR**

The FT-IR spectroscopy was used as a supplementary technique in order to investigate the possible chemical interaction between drug–excipient and to confirm the results obtained by the thermal analysis. It is the most suitable technique of the non-destructive spectroscopic methods and has become an attractive method in the analysis of pharmaceutical solids, since the materials are not subject to thermal or mechanical energy during sample preparation, therefore preventing solid-state transformations. The appearances of new absorption band(s), broadening of band(s), and alteration in intensity are the main characteristics to obtain the results recherched.

The FT-IR spectra are presented in figures 6-9 and the main absorption bands are summarized in table 3.

The main differences resulting from comparing the spectrum of IB with the spectra of IBPAD, IBRP and IBCIPLA are presented below, as follow:
- the considerable broadening and the increase (≈20% for IBRP) of the bands from the region 3500 – 3000 cm⁻¹, attributed to the OH group present in the IB molecule (carboxyl group) as well as in the excipients: starch, microcrystalline cellulose, methylcellulose, lactose monohydrate;

- the significant increase (≈25% for IBCIPLA and 40% for IBRP) of the intensity for the three bands from the region 2955 – 2869 cm⁻¹ that correspond to the methylene, respectively methyl group from IB as well as the excipients: microcrystalline cellulose, methylcellulose, polividone K30, magnesium stearate;

- the increase of the intensity (≈15% for IBRP, respectively IBCIPLA) for the most intense band (1720 cm⁻¹) which represents the carbonyl vibration band from IB as well as the excipients: povidone K30, magnesium stearate;

- the increase of the intensity for the bands presents in the region 1508 – 1420 cm⁻¹, respectively 1321 – 1184 cm⁻¹ (24% for IBCIPLA and 34% for IBRP, respectively 20% for IBCIPLA and 23% for IBRP), which correspond to the methyn, methylene, OH, COO (asymmetric, respectively symmetric vibrations);

- the increase of the intensity (10 – 15%) of the bands from 936 cm⁻¹, respectively 865 cm⁻¹ which correspond to the vibration of Si–O and C–N;

- the increase of the intensity 4% for the band from 780 cm⁻¹ (7%, 22% respectively 25%), which corresponds to the phenyl ring;

- the disappearance of the band from 2360 cm⁻¹ (IB) in the spectra of IBPAD and IBRP;

- the appearance of the lots of band in the spectra of IBPAD; IBRP and IBCIPLA as follows: 3044; 3021 and 3019; 2979; 2850; 1167 and 1121; 1091; 1034; 849; 479 cm⁻¹.

On the basis of mentioned differences it may be considered that the composition of the studied compounds is different.

From the FT-IR spectra and wave number where characteristic bands appear, the active substance and its pharmaceutical forms can be easily differentiated.

**X-ray analysis**

To investigate the thermal behaviour of IB and correspondent pharmaceuticals: IBPAD, IBRP and IBCIPLA, besides the FT-IR spectroscopy which is a qualitative analysis technique, the X-ray powder diffraction has been used for qualitative and quantitative identification of crystallinity. The number of the specialty articles which used the X-ray powder diffraction is growing [46-51].

By the comparison of diffractogram of IB with the diffractograms of pharmaceutical compounds correspondents, the appearance of new lines or the disappearance of some of the diffraction lines of higher, moderate and lower intensities from IB, respectively the modification of the intensity for certain lines presented in IB, indicates the differences of the studied compounds. The X-ray diffraction data for the studied compounds are presented in tables 4–7.

By the comparing the data from Tables 4–7 on constants great differences between these, by the disappearance of certain lines from IB–AS diffractogram, the appearance of the new lines in diffractograms of IBPAD, IBRP and IBCIPLA, respectively, the modification of intensity for ceratins lines present in the IB–AS diffractogram.

These differences indicate a different composition between IB–AS respectively, pharmaceuticals correspondent: IBPAD, IBRP and IBCIPLA.
Conclusions

The ibuprofen active substance (IB–AS) and three of the pharmaceutical products correspondents: IBPAD; IBRP and IBCIPLA were simultaneously characterized by thermal analysis, FT-IR spectroscopy and X-ray diffraction patterns.

The thermal behaviour of the four compounds has been investigated by the TG/DTG and DTA techniques. From the thermoanalytical curves were observed significant differences between the curves of the pure compound and those of the pharmaceutical products.

Also, between the FT-IR spectra and X-ray diffractograms of the two compounds categories there are significant differences.

The melting point is commonly used as a preliminary identification parameter for crystalline organic compounds. In comparison with the melting point determined by using the classical methods, the determination under a dynamic flow of dry nitrogen can provide a reliable value for the fusion temperature.

This justifies the usage of DSC(DTA) as a routine technique for the identification and quality control of the active substance created for pharmaceutical usage, by melting point.

A considerable effect of heating rate on the thermal decomposition of studied compounds may be due to a complexity of the thermal rearrangement of examined compounds to the intermediate products.

The simultaneous analysis of the TG-DTG-DTA, FT-IR and X-ray data constitutes a credible and secure method of control and just evaluation in the practice of the pure and pharmaceutical compounds.

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