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CHARACTERIZATION OF PHARMACEUTICALS BY THERMAL ANALYSIS

CARACTERIZAÇÃO DE FÁRMACOS POR ANÁLISE TÉRMICA

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ABSTRACT

Thermogravimetry (TG), derivative thermogravimetry (DTG) and differential scanning calorimetry (DSC) were techniques used in this work to study thermal behavior of some analgesics: antipyrin, dipyrone and paracetamol. The results led to thermal stability data and also to interpretations concerning thermal decomposition. These techniques seem promising in quality control of active ingredients, excipients, etc., for the pharmaceutical industry.

Key words: thermal behavior; stability; TG; DSC; quality control

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1. Introduction

Thermal Analysis is the term used to describe the analytical techniques that measure the physical and chemical properties of a sample as a function of temperature or time. The sample is subjected to a temperature program, which consists of a series of pre-selected segments in which the sample is heated or cooled at a constant rate or held at a constant temperature. In many experiments the atmosphere is also of importance. In particular, one distinguishes between the use of inert and oxidizing gases.

The potential applications of thermal analysis (FORD et al., 1989; WENDLANDT, 1986) in the pharmaceutical industry are numerous on account of the chemical-physical aspects of investigations. Amongst others these include the method of development, characterization and specification of active or inactive ingredients, safety analysis or routine analysis in quality control and stability studies.

Pharmacy is the science that concerns itself with the nature, the action, the preparation and the delivery processes of pharmaceutical preparations. In contrast, the pharmaceutical industry is concerned mainly with the development and production of pharmaceutical preparations.

Pharmaceutical preparations (FORD et al., 1989; GIRON, 1986; SCHNITZLER et al., 2001) 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, rectal, etc.) and the physico-chemical properties of the drug are suitable. 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 right proportions.

Considering the number of physical parameters of a substance which may be measured, the number of techniques derived is very large. Two books dealing with the principle, instrumentation and applications of Thermal Analysis methods are Ford et al., 1989 and Wendlant, 1986. Thermogravimetry (TG) measures the mass of a sample which is subjected to a temperature program. The measurement is performed in a defined atmosphere, usually in inert conditions (nitrogen) or in an oxidative

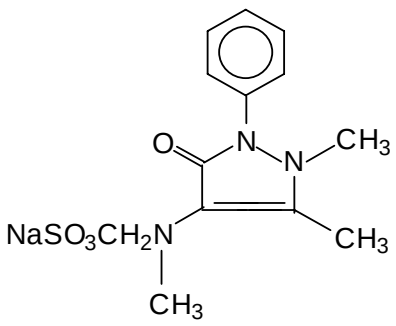
environment (air or possibly oxygen). The mass is measured with a highly sensitive electronic balance. Interfering buoyancy or gas flow effects are compensated by a blank curve correction. Thermogravimetric analysis provides information on the content volatile components such as solvents or water, on decomposition behavior and on the ash or filler content. Derivative Thermogravimetry (DTG) is the mathematical procedure that supplies the first derivative of a TG curve; this technique is important to facilitate the calculations supplied by the TG curve. Differential Scanning Calorimetry (DSC) measures the difference between the heat flows to the sample and the reference pan that flows subjected to the same temperature program. A heat flow corresponds to transmited power and is measured in watts (W) or milliwatts (mW). If the heat flow of power is integrated with respect to time then a quantity of energy is obtained which is expressed in units of mWs = mJ. If the sample absorbs energy then the enthalpy change is called endothermic (peak down). If the sample liberates energy then the enthalpy change is said to be exothermic (peak up). DSC measurements provide informations on thermal effects which are characterized by an enthalpy change and by the temperature range, such as melting behavior, crystallization, solid-solid transitions and chemical reactions. Since the specific heat capacity is also measured, a change in heat capacity such as that which occurs at the glass transition can also be determined.

2. Experimental

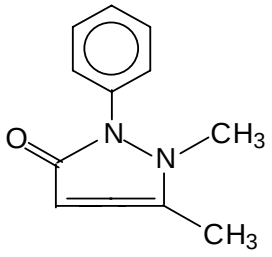
The thermal behaviors of some drugs (active ingredients) are shown in Figures 2 – 6. This work was done with the active ingredients: antipyrine, dipyrone and paracetamol, using the techniques, thermogravimetry (TG), derivative thermogravimetry (DTG) and differential scanning calorimetry (DSC), which allowed us to verify the thermal behavior of these compounds.

TG, DTG and DSC were obtained by using a simultaneous thermobalance SDT 2960 (TA Instruments-UEPG) with a nitrogen flow of 70 mL/min, heating rate of 20 ºC/min, and with a sample weighing about 8 – 10 mg. An open α-Al_2O_3 crucible was used. These techniques allowed us to obtain results on the thermal behavior of these analgesic agents.

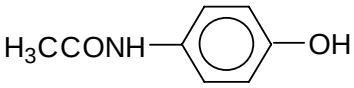
The compounds studied are shown in Figure 1:



Dipyrone
[(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)methylamino]methanesulfonic acid



Antypipyrin
1,2-dihydro-1,5-dimethyl-2--phenyl-3H-pyrazol-3-one



Paracetamol
N-(4-Hydroxyphenil)acetamide

Figure 1: Structural formulas of dipyrone, antipyrin and paracetamol.

3. Results and discussion

All the analgesics studied in this work by the thermoanalytical techniques were submitted to the same experimental conditions, and shown in Figures 2 –7. TG curves of antipyrine and paracetamol show mass loss in a single stage, and of dipyrone in four stages, although antipyrine and dipyrone belong to the same group.

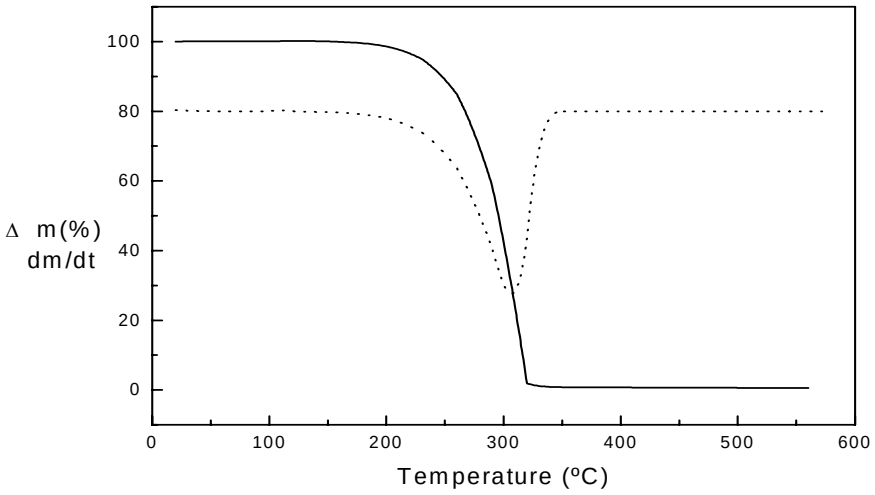


Figure 2: TG (solid line) and DTG (dot line) curves of antypirine , obtained in dynamic atmosphere of N_2; flow of 70 mL/min; heating rate 20 ºC/min; α-Al_2O_3 crucible.

The DSC curve of this compound is shown separately in Figure 3, with the calculated enthalpy of each phenomenon.

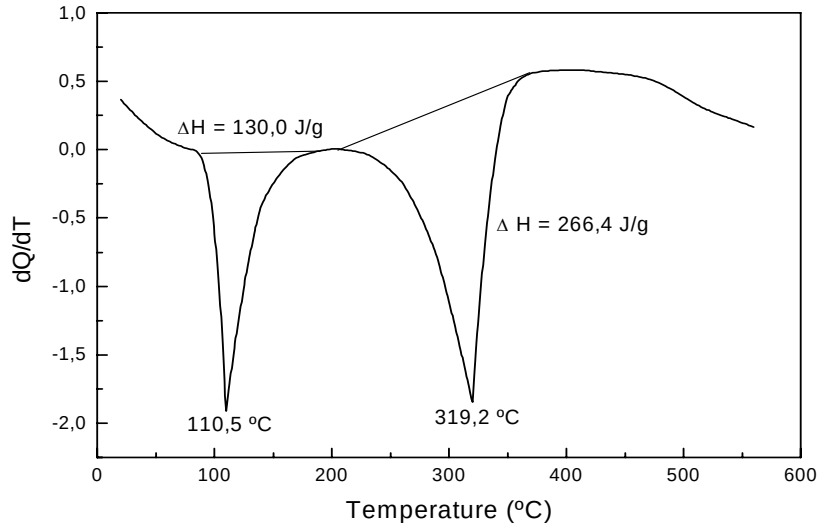


Figure 3: DSC curve of antypirin sample, obtained in a dynamic atmosphere of N_2; flow of 70 mL/min; heating rate 20 ºC/min; α-Al_2O_3 crucible.

The first endothermic peak is due to melting at 110,5 ºC, with ΔH = 130,0 J/g, and the second endothermic peak is due to the thermal decomposition according to the TG curve to 319,2 J/g with ΔH = 266,4 J/g.

The TG curve (solid line - Figure 2) shows mass loss in a single stage up to 323 ºC according DTG curve (dot line - Figure 2)

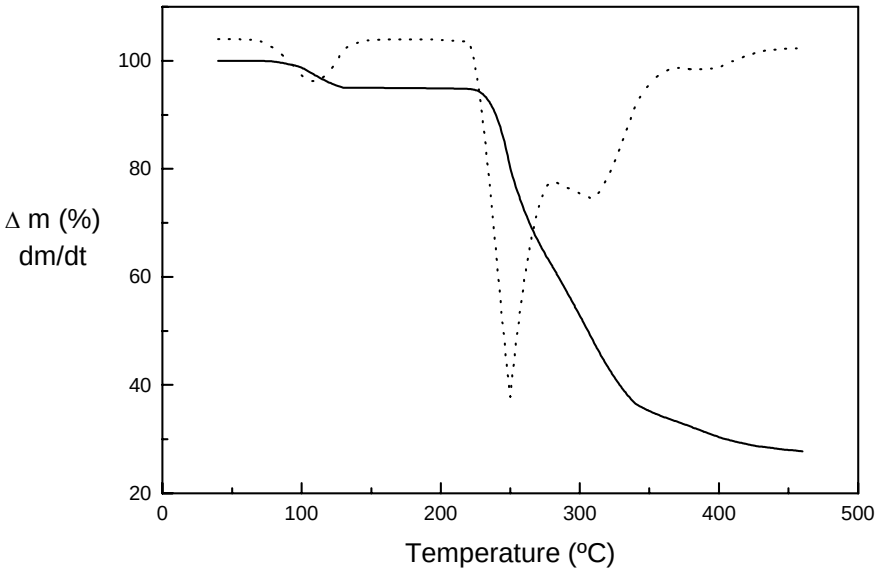


Figure 4: TG (solid line) and DTG (dot line) curves of dipyrone sample, obtained in dynamic atmosphere of N_2; flow of 70 mL/min; heating rate 20 ºC/min; α-Al_2O_3 crucible.

The TG curve of dipyrone (solid line - Figure 4) indicates the first mass loss (5,012 %) at 91 to 170 ºC due to dehydration, being the compound monohydrate. The other mass losses occur in consecutive stages up to 480 ºC with mass loss of 67,58% of anhydrous compound. The DTG curve (dot line) is the mathematical procedure that confirms the results obtained by the TG curve.

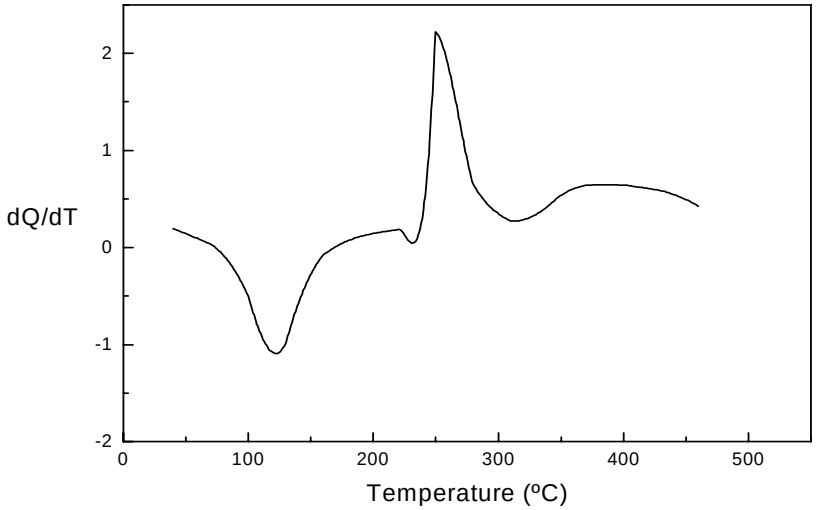


Figure 5: DSC curve of dipyrone sample, obtained in dynamic atmosphere of N_2; flow of 70 mL/min; heating rate 20 ºC/min; α-Al_2O_3 crucible.

The DSC curve shows an endothermic peak according to the TG curve due to dehydration of dipyrone (ΔH = 152,3 J/g). The sharp endothermic peak at 233 ºC is due to the fusion, and it is followed by a sharp exothermic peak at 256 ºC ascribed to the thermal decomposition in consecutive stages.

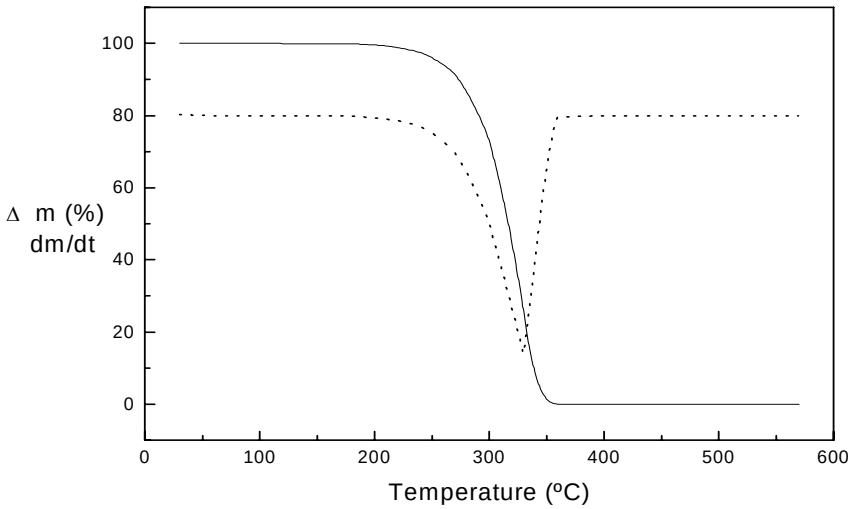


Figure 6: TG (solid line) and DTG (dot line) curves of paracetamol sample, obtained in dynamic atmosphere of N_2; flow of 70 mL/min; heating rate 20 ºC/min; α-Al_2O_3 crucible.

TG curve of paracetamol allows us to verify that the compound is anhydrous and show mass loss in one stage only, up to 326ºC, with total mass loss.

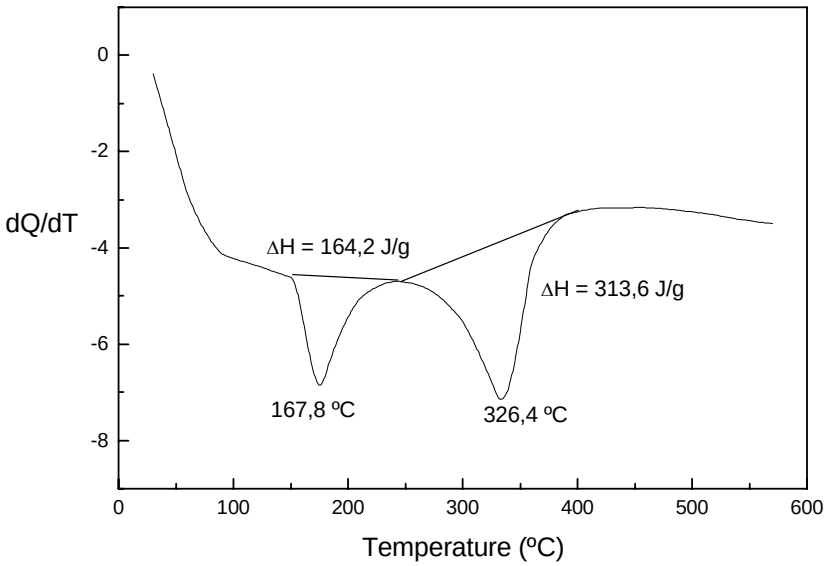


Figure 7: DSC curve of paracetamol sample, obtained in dynamic atmosphere of N_2; flow of 70 mL/ min; heating rate 20 ºC/min; α-Al_2O_3 crucible.

DSC curve shows the first endothermic peak due to fusion of the compound at 167,8 ºC (ΔH = 164,2 J/g) and the second endothermic peak due to thermal decomposition at 326,4 ºC.(ΔH = 313,6 J/g).

4. Conclusions

Thermal analysis techniques provide a set of useful techniques for the characterization of phermaceutical materials from the raw materials or finished products.

The thermoanalytical techniques used in this work were

Thermogravimetry (TG) allowed studies on the thermal decomposition (mass loss) and thermal stability of same analgesics. Differential Scanning Calorimetry (DSC) is a technique of great usefulness in the characterization and quality control of pharmaceuticals such as active ingredients, excipients, raw materials, packaging materials, etc. It is valuable for the quantitative measurement of the water and hydration waters, thermal decomposition (mass loss) and thermal stability of the compounds studied. The endotherm or exotherm phenomenon (peak down and peak up respectively) were observed and the enthalpies were calculated in each process, since the same experimental conditions were adopted.

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RESUMO

Termogravimetria (TG), termogravimetria derivada (DTG) e calorimetria exploratória diferencial (DSC) foram técnicas usadas neste trabalho para estudar o comportamento térmico de alguns analgésicos: antipirina, dipirona e paracetamol. Os resultados conduziram aos dados sobre estabilidade térmica e também a interpretações concernentes à decomposição térmica. Essas técnicas mostram-se promissoras no controle de qualidade de princípios ativos, excipientes, etc., para a indústria farmacêutica.

Palavras-chave: comportamento térmico; estabilidade; TG; DSC; controle de qualidade

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REFERENCES

1 FORD, J. L; TIMMINS, P. **Pharmaceutical Thermal Analysis - Techniques and Applications**. New York: Ellis Horwood, 1989.

2 GIRON, D. **J. Pharm. & Biomed. Anal**. 4, (6), 755, 1986.

3 RADECKI, A.; WESOLOWSKI, M. **J. Therm. Anal.** 17, 73, 1979.

4 RIBEIRO, Y. A.; CAIRES, A. C. F.; BORALLE, N.; IONASHIRO, M. **Therm. Acta**. 279, 177, 1996.

5 SCHNITZLER, E.; CARVALHO-FILHO, M. A. S.; STADLER, C. C.; VOLPATO, A. M.; IONASHIRO, M. **Ecl. Quím**. 26, 41, 2001.

6 WENDLANDT, W. W. **Thermal Analysis**. John Wiley & Sons., N. York, 1986.

7 WENDLANDT, W. W.; COLLINS, L. W. **Anal. Chim. Acta.** 71, 411, 1974.

9 WENDLANDT, W. W.; HOIBERG, J. A. **Anal. Chim. Acta**. 29, 539, 1963.

10 WESOLOWSKI, M. **Acta Pharm. Jugosl**. 32, 303, 1982.

11 WESOLOWSKI, M. **Mikrochim. Acta**. 1, 199, 1980.

12 WESOLOWSKI, M. **Therm. Acta.** 209, 223, 1992.