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DSC IN THE CHEMICAL ANALYSIS OF DRUGS
Determination of diclofenac in pharmaceutical formulations

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Abstract

Differential scanning calorimetry was applied to the determination of diclofenac in three 'Voltaren' formulas. The pharmaceutical products (soluble tablets, suppositories and vials) were selected in order to show that calorimetric analysis is an easy technique to perform and can be competitive with other conventional methods.

In the tablets diclofenac (DH) was determined, without any pre-treatment, from the area of the endothermic peak which occurs at about 180°C in the DSC curve obtained in N_2 atmosphere. In the analysis of the suppositories and vials, nitrilotriacetic acid (NTA) was added to transform the diclofenac sodium salt (DS) into the thermally active form (DH). In both cases, it was necessary to eliminate the interference of excipient by cyclohexane extraction (suppositories) or by a multistep program for the DSC run (vials).

The accuracy of the results and the simplicity of the procedure justify the important role of DSC in the analysis of these drugs and certainly of several other commercial products.

Keywords: diclofenac, DSC

Introduction

Differential scanning calorimetry (DSC) is the most widely used thermoanalytical technique for studying and characterising a wide variety of materials. However, in spite of the quantitative data (transition temperature, heat capacity and enthalpy) that can be obtained, this technique is seldom applied to the dosage of the major ingredients of commercial products. In our opinion this is because both the following conditions must be present: a) the analyte must have a characteristic, well shaped calorimetric peak; b) the other components must not influence the area of this peak.

The DSC technique plays an important role in our research program, which has recently focused on new methods in food and pharmaceutical analysis [1–6]. In the most recent paper [6], we have reported the thermal behaviour of diclofenac (DH), the active ingredient of several important pharmaceutical formulations. It is evidenced how this drug, unlike its salts, exhibits an apparent single thermal process when it is heated up to 250°C in nitrogen atmosphere. Both the TG and DSC curves

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each actually showed a 100% mass loss and only one endothermic peak, the area of which was proportional to the drug concentration (ΔH=98.3 J g^{-1}). On this basis, we proposed a calorimetric procedure to determine diclofenac sodium (DS) in 'Voltaren 50' tablets. However, because of the delicate pre-treatment of the sample required to transform the DS into the DH form and to eliminate the interfering species, it is recommended only for particular purposes.

The aim of the present study is to show that a simple treatment of the sample may sometimes be sufficient to obtain excellent results in the DSC determination of an ingredient that does not respect the conditions specified above. We, therefore, extended the calorimetric method to the analysis of three other 'Voltaren' formulations.

Experimental

Materials

Diclofenac sodium salt (DS) was a pure grade product ('Sigma') and used without further purification. The purity of the dry material was checked by potentiometric titration. A standard DS solution was prepared by dissolving about 150 mg of the (accurately weighed) pure drug in water and diluting to 10 mL.

Diclofenac (DH) was prepared as described in [6].

Voltaren soluble tablets ('Ciba-Geigy'), Voltaren suppositories ('Ciba-Geigy') and Voltaren vials ('Novartis Farma') were commercial products.

All other chemicals were analytical-reagent grade.

Apparatus

Thermal measurements were carried out by using a Perkin Elmer TGS-2 thermal analyser, connected to a model 3700 Data Station, and a 1020 series DSC-7 Thermal Analysis System equipped with multitasking software for instrument control and data analysis (particularly, by processing the calorimetric curve, it calculates the relative enthalpy variation (J g^{-1}) connected with the different endo–exo events). Unless otherwise specified, thermogravimetry and differential scanning calorimetry runs were made on samples containing about 1–2 mg (TG) and 0.3–0.5 mg (DSC) of the active compound, in a stream of N_2 (flow rate, 50 ml min^{-1}), heating rate 10°C min^{-1}.

Results and discussion

Taking the results of previous trials [6] into account, we split this study into the following three steps.

Optimisation of DSC runs

To reduce the time of the analysis without affecting its accuracy, we first investigated in depth the thermal behaviour of DH, determining the narrowest temperature range for DSC runs. Although the endothermic process begins at about 165°C, an initial

temperature not exceeding 100°C is nevertheless recommended to avoid the partial decomposition of diclofenac in air when the pan is placed in the calorimetric cell. In the end, the run may be stopped at 200°C because the peak is reached just before 190°C. These new experimental conditions made it possible to distinguish two thermal processes taking place consecutively, but partly overlap, when DH is heated in nitrogen atmosphere. In fact, by comparing TG and DSC curves we found the sublimation of diclofenac starts at about 165°C. The evaporation takes place at a maximum rate at 230°C, without any noticeable change in enthalpy. For this reason, the observed endothermic peak (t_p=182°C) must be assigned to the melting process of the drug. The correctness of this statement is supported by the monitoring of the gaseous products evolved in runs (interfacing TG to FT-IR) and by the analysis of the residue or the sublimate obtained in DSC runs (heating interrupted at appropriate temperatures in the range between 150 and 250°C).

Transformation of the drug into the thermally active form

Seeing that a diclofenac sodium salt (DS) is generally used in the commercial products, the next step was to find the most appropriate procedure to transform the drug into the acid form (DH). Among the inorganic and organic reagents tested, nitrilotriacetic acid (NTA) appeared to have both characteristics required. It is a stronger acid than diclofenac and does not interfere in the calorimetric analysis because of its thermal stability in the temperature range concerned. Indeed, no mass loss (TG) or enthalpy variation (DSC) occur up to about 225°C (Fig. 1).

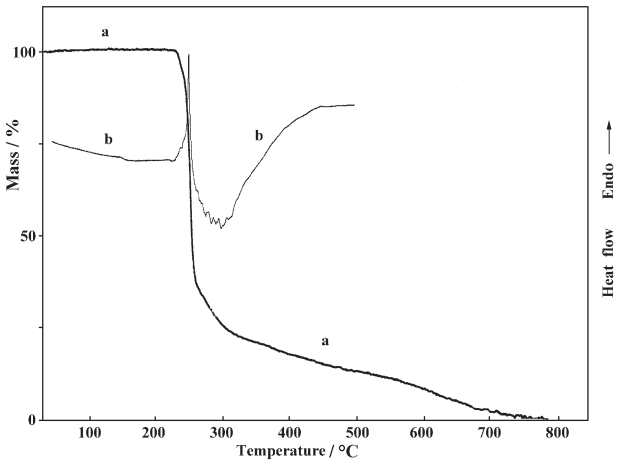

Fig. 1 TG (curve a) and DSC (curve b) in nitrogen of nitrilotriacetic acid (NTA)

The following procedure was thus carried out to check the method: in a 40 μL capacity aluminium pan, the standard DS solution (20 μL) and NTA reagent (4–6 mg) were mixed with a steel needle [this system of homogenisation represents the result of a compromise between desirable operational simplicity and the possible losses of

precision and/or of accuracy of the results. The experimental proofs have underlined that, operating with adroitness, neither of the aforesaid factors seem to suffer too much, resulting more than acceptable]. The mixture was dried in an oven (80°C) and the DSC run performed up to 200°C under the conditions described in the apparatus section. The recovery (R%) of DS was calculated by the formula

$$R(\%)=(\Delta H/\Delta H_0)(100/C) \quad (1)$$

where ΔH is the change of enthalpy (J mL^{-1}) measured, ΔH_0 is that calculated for a pure DS (91.5 J g^{-1}) [6] and C is the concentration (g mL^{-1}) of DS in the standard solution (the overall results are reported in Table 1).

Table 1 Validation of accuracy and precision of the proposed method (experimental as reported in 'Transformation of the drug...')

DS (standard solution)	ΔH/J mL^{-1}	DS/mg mL^{-1}	Recovery/%
16.69 (mg mL^{-1})	1.53	16.72	100.18
	1.51	16.50	98.86
	1.55	16.94	101.50
	1.48	16.17	96.88
	1.51	16.50	98.86
	1.55	16.94	101.50
	1.54	16.83	100.84
average*	1.524	16.66	99.80
S_x	0.026	0.28	1.70
S_x^-	0.010	0.11	0.64

*S_x and S_x^- are the estimated standard deviation and the estimated standard deviation of the mean

The quantitative recovery of the drug (99.8%) was proof of the full conversion of DS and the absence of interference by NTA added in large excess (NTA/DS molar ratio>30). However, in these conditions, the calorimetric peak may slightly be larger

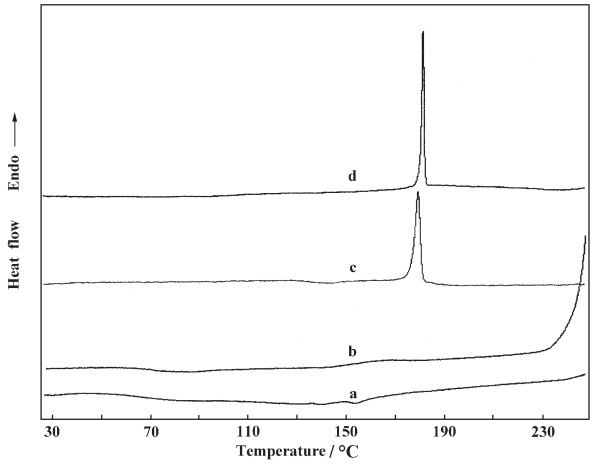

Fig. 2 DSC in nitrogen of DS (curve a), NTA (curve b), DS+NTA (curve c) and DH (curve d)

and occurs at a lower temperature ($t_p \approx 178°C$) than that found for pure diclofenac. The DSC curves of DH, DS, NTA and DS+NTA mixture, in the temperature range of the analysis, are reported in Fig. 2.

Determination of diclofenac in pharmaceutical formulations

The experimental procedure of the analysis referring to the chemical and/or thermal pre-treatment of the sample, cannot be fully generalised because it depends on the composition of the different proprietary medicines. For this reason, a specific procedure was proposed and discussed for each of the formulations analysed. The overall results, collected in Table 2, support those obtained by UV [6] and Visible [7] methods and demonstrate the quantitative recovery of the active ingredient in all the products analysed.

Table 2 Determination of the diclofenac in pharmaceutical formulations

Sample	Content of the diclofenac (as sodium salt)			
	Labelled	Found*		
		UV [6]	Vis. [7]	DSC
Tablets	50 (mg per tablet)	51.33	52.14	51.33
		51.23	51.52	49.44
		50.47	51.58	51.59
		50.49	52.86	51.33
		51.46	51.41	50.41
	average	51.00	51.90	50.82
	S_x	0.48	0.61	0.89
	S_x^-	0.21	0.27	0.40
Suppositories	100 (mg per suppository)	101.81	100.73	101.49
		100.67	101.87	99.37
		100.88	101.66	100.67
		101.64	100.40	99.91
		100.49	102.05	101.62
	average	101.10	101.34	100.61
	S_x	0.62	0.73	0.98
	S_x^-	0.28	0.33	0.44
Vials	75 (mg per vial)	77.97	76.99	77.30
		76.48	77.05	77.15
		76.84	77.76	76.02
		77.74	78.01	76.05
		76.69	76.75	77.50
	average	77.14	77.31	76.81
	S_x	0.67	0.54	0.71
	S_x^-	0.30	0.24	0.32

*S_x and S_x^- are the estimated standard deviation and the estimated standard deviation of the mean

Tablets

'Soluble Voltaren' nominally contains 46.5 mg of diclofenac (DH) per tablet (corresponding to 50 mg of DS) and the following excipients: cellulose microcrystalline, precipitated silica, sodium carboxymethylstarch, sodium carboxymethylcellulose, hydrogenated castor oil and talc.

A preliminary investigation of this product proved that the active ingredient may be determined without any pre-treatment because it is already in DH form and the excipients, in N_2 atmosphere, are all thermally stable up to 250°C (Fig. 3 curve a).

Therefore, the following more simple procedure may be performed.

Determine the average mass of a tablet (W) by weighing at least 5 tablets. Weigh accurately about 5 mg of the previously powdered sample into an aluminium pan. Perform the DSC run up to 200 °C applying the conditions described in the apparatus section. Calculate the concentration (C, mg per tablet) of DH by the formula

$$C=(\Delta H/\Delta H_0)W \quad (2)$$

where ΔH is the change of enthalpy (J g^{-1}) measured and ΔH_0 is that determined with a pure DH standard (98.3 J g^{-1}) [6].

Suppositories

'Voltaren 100' nominally contains 100 mg of diclofenac sodium (DS) per suppository and the following excipients: solid semi-synthetic glycerids.

The DSC curve of this product (Fig. 3 curve b) showed only the fusion peak of glycerids (in nitrogen atmosphere, DS is stable up to about 265°C), but this process interferes with diclofenac determination because, on adding NTA, the curve remains unchanged.

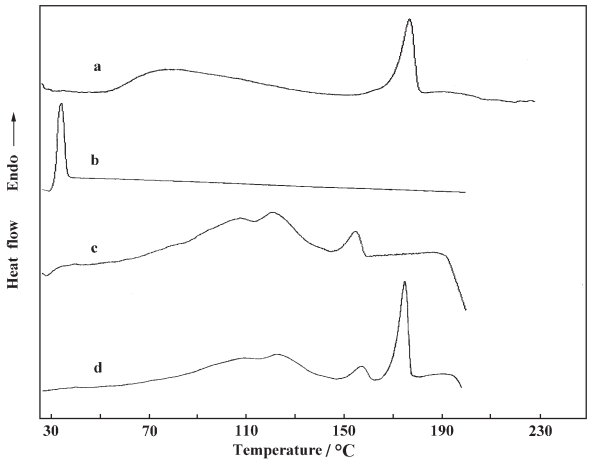

Fig. 3 DSC in nitrogen of Voltaren soluble tablets (curve a), Voltaren suppositories (curve b) and Voltaren vials without (curve c) and with (curve d) NTA added

To fully transform DS into DH form and to avoid matrix interference, the following procedure is recommended.

Determine the average mass of a suppository (W) by weighing at least 5 suppositories. Weigh accurately about 500 mg (W_0) of the sample, previously homogenised by heating it on a water-bath until it is completely melted and then allowed to cool, while stirring. Extract the glycerids into about 5 mL of cyclohexane and wash the residue (DS) twice with 2–3 mL of this solvent. Dry the residue under reduced pressure and dissolve it in 2.00 mL (V) of water. Place exactly 20 μL of this solution and about 5 mg of NTA in a 40 μL capacity aluminium pan. Mix with a steel needle and dry the mixture in oven (80°C). Perform the DSC run up to 200°C, applying the conditions described in the apparatus section. Calculate the concentration (C, mg per suppository) of DS by the formula

$$C=V\,(\Delta H/\Delta H_0)\,(W/W_0) \tag{3}$$

where ΔH is the change of enthalpy (J mL^{-1}) measured and ΔH_0 is that calculated for a pure DS.

Vials

'Voltaren Vials' nominally contains 75 mg of diclofenac sodium (DS) per vial (3 ml) and the following excipients: mannitol, sodium metabisulphite, benzyl alcohol, propylene glycol, sodium hydroxide, water for injection.

The DSC curve of the product, oven dried at about 80°C, showed endothermic peaks up to about 160°C and an exothermic process beginning above 190°C (Fig. 3 curves c). This series of endo–exo events are difficult to assign because of the complexity of the matrix. In the presence of NTA, the peak of DH melting (Fig. 3 curves d) was also evident but the enthalpy value may be influenced by the neighbouring endothermic process. Luckily the latter is an irreversible transition and its interference may be eliminated by the following procedure.

Place 20 μL of the sample and about 5 mg of NTA in a 40 μL capacity aluminium pan. Mix with a steel needle and oven dry the mixture (80°C). Using the general conditions reported in the apparatus section, execute the following multistep program for the DSC run. Heat the dried mixture to 160°C, stop the temperature increase for 2 min and, after cooling to 150°C, complete the DSC curve by heating up to 200°C. Calculate the concentration (C, mg mL^{-1}) of DS by the formula

$$C=(\Delta H/\Delta H_0) \tag{4}$$

where ΔH is the change of enthalpy (J mL^{-1}) measured and ΔH_0 is that calculated for a pure DS.

Conclusions

DSC can be a very suitable technique for the analysis of drugs and many other commercial products.

The proposed method provided consistent values in the analysis of the test products. It was also accurate, fairly rapid, easy to perform and, apart from the actual instrument, comparatively inexpensive. One simple treatment of the sample (none in the case of the soluble tablets) was sufficient to prevent the interference of the other components and/or to transform the analyte (DS) into a thermally active compound (DH).

Although the selection of the three products analysed was influenced by the aim of our investigation (i.e. the extensive application of DSC technique to the quantitative chemical analysis of drugs) they were nevertheless commercial products required to assay the major ingredients during the entire manufacture process, from raw material testing to the analysis of the final product.

In view of the results we consider it desirable to promote research aimed at the chemical analysis of drugs as well as the study of formulations containing excipients which, for equal performance, do not interfere in the analytical control of the product.

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