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Determination of oxybuprocaine HCL in pharmaceutical formulations using thermal techniques

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ABSTRACT

The thermal behavior of oxybuprocaine hydrochloride (OXY) has been studied. Thermogravimetric analysis (TGA), derivative thermogravimetry (DTG) and differential thermal analysis (DTA) techniques were used to study the thermal behavior of the drug.

Thermal-analytical study showed that OXY is thermally decomposed in four steps. The first step occurs in the temperature range of 62.05- 166.70 ºC, the second step occurs at 166.70 -354.91 ºC, the third step occurs at 354.91 - 455.52 ºC and the fourth step at 455.52–489.05 ºC. Melting point of OXP was recorded at 160.15 ºC.

Thermodynamic parameters such as activation energy (Ea), frequency factor (A), reaction order (n), and correlation coefficient (r) were calculated using different kinetic models. The purity value for the drug was found to be 99.36%. Thermal analysis technique gave satisfactory results to obtain quality control parameters such as melting point, water content and ash content in comparison to those obtained using official methods. Thermal analysis justifies its application in quality control of pharmaceutical compounds due to its simplicity, sensitivity and low operational costs. DSC results indicated that the degree of purity of Oxybuprocaine HCl is similar to that found by official method.

KEYWORDS

Oxybuprocaine HCl;
Thermal analysis (TG/DTG, DTA);
Differential scanning calorimetry (DSC);
Purity.

INTRODUCTION

Oxybuprocaine hydrochloride (OXY) or benoxinate HCl is 2-diethylamino ethyl 4-amino-3-butoxybenzoate hydrochloride Figure 1. It is a para aminobenzoic acid ester local anesthetic used for surface anaesthesia as the hydrochloride in 0.4% solution in short ophthalmological procedures or solution of oxybuprocaine hydrochloride (1%) is used for surface anesthesia of the ear, nose and throat[1].

OXY could be determined using several analytical methods including spectrophotometric methods[2-6], HPLC[6,7-12], TLC[13], GC[14,15], electrochemical techniques[16-18], DSC on dosage form[19] and titrimetric method[20]. OXY is a para aminobenzoic acid ester and is therefore susceptible to environmental degradation. Only one DSC method was reported for determination of the purity of OXY in dosage form therefore; the aim of this work was to evaluate the thermal characterization of OXY using a variety of techniques including TG/

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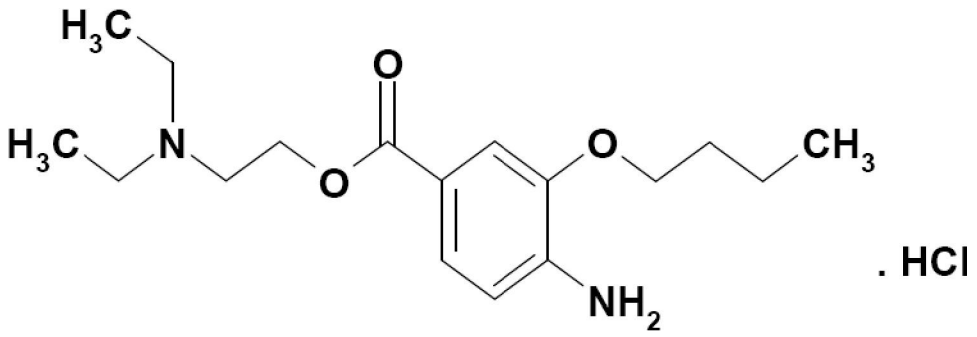

Figure 1 : Chemical structure of oxybuprocaine HCl.

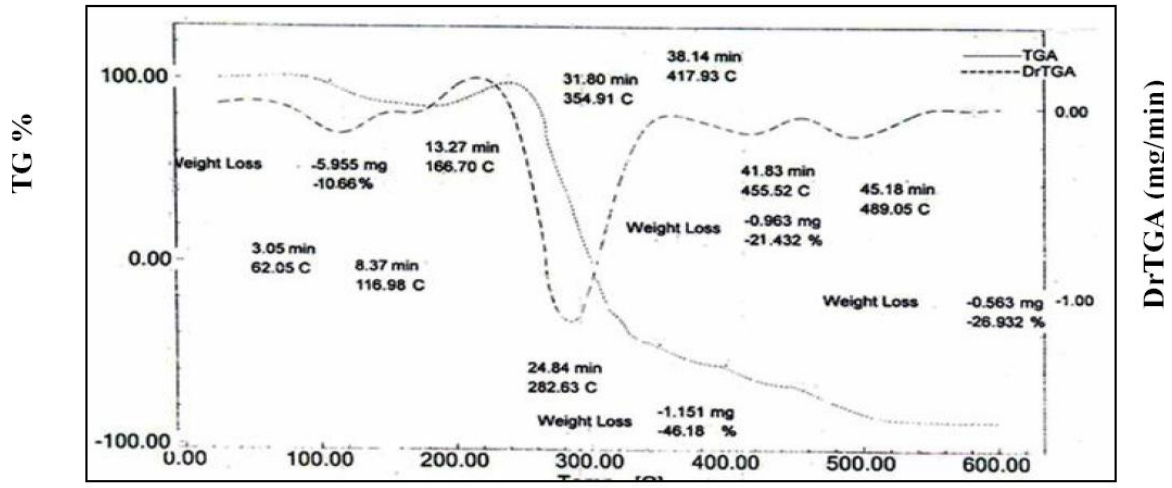

Figure 2 : TG/DTG thermo-gram of oxybuprocaine HCl.

DTG, DTA and DSC and comparing the obtained result with those obtained by official method.

MATERIAL AND METHODS

Material

Oxybuprocaine hydrochloride and Benox eye drops® (Batch No. (17468) labeled to contain 0.4% OXP) were kindly supplied by Egyptian International Pharmaceutical Industries Company (EPICO), 10th of Ramadan city, Egypt. Purity of OXY was found to be 99.79 ± 0.619 according to the official method[20].

Methods

Thermogravimetry, Derivative thermogravimetry (TG/DTG) and Differential thermal analysis (DTA)

TG/DTG and DTA curves of OXY were recorded using Simultaneous Shimadzu Thermo-Gravimetric Analyzer TGA-60 H (Tokyo, Japan), with TA 60 software in dry nitrogen atmosphere at a flow rate of 30 mL/min in platinum crucible containing aluminum oxide as a reference substance. The experiments were performed from ambient temperature up to 600 ºC with a heating rate of 10ºC/min. The sample mass was about 5 mg of the drug without any further treatment.

Differential scanning calorimetry (DSC)

The DSC curves of OXP were recorded using Shimadzu-DSC 50 (Tokyo, Japan), in dynamic nitrogen atmosphere with a constant flow of 30 mL/min, and heating rate of 10ºC/min, up to temperature 300ºC. The sample with a mass of about 1.80 mg was packed in platinum pan. DSC equipment was preliminarily calibrated with standard reference of indium. The purity determination was performed using heating rate of 10ºC/min in the temperature range from 25 to 200 ºC in nitrogen atmosphere.

The kinetic parameters

The kinetic parameters of decomposition such as,

TABLE 1 : Thermal decomposition data of TG, DTG, and DTA, curves of oxybuprocaine hydrochloride.

Temperature range (°C)	DTG max (°C)	Mass loss %	Assignment	DTA (°C)
62.05- 166.70	116.98	10.66 %	loss of HCl molecule and melting	161.95
166.70 -354.91	282.63	46.18 %	loss of $C_7H_{14}N_2O_2$ molecule	278.70
354.91 - 455.52	417.39	21.3 %	loss of C_4H_9O molecule	------
455.52– 540.12	489.05	26.93 %	loss of C_6H_5O molecule	488.77

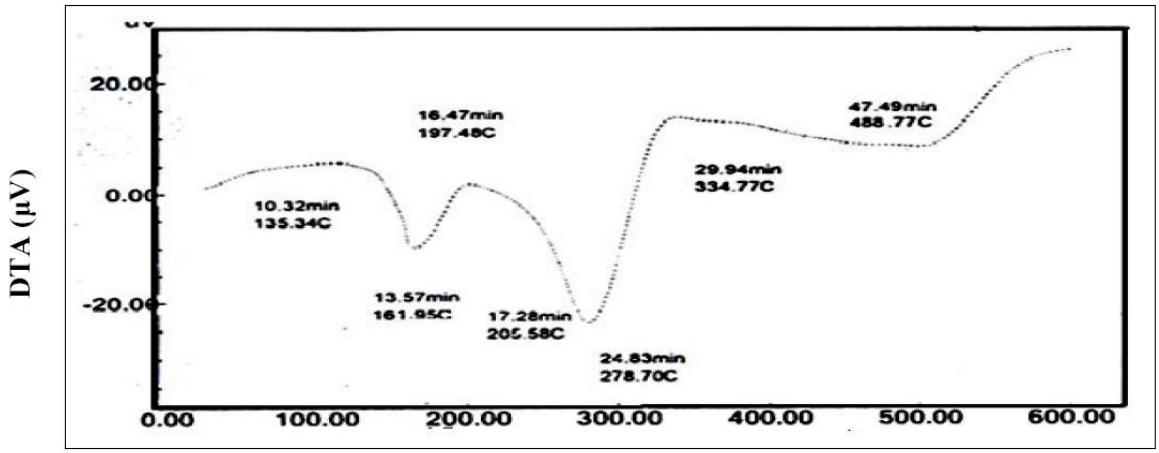

Figure 3 : DTA thermo-gram of oxybuprocaine HCl.

activation energy (Ea), frequency factor (A), and reaction order (n) were calculated from TG/DTG curves. The mathematical models of Horowitz with Metzger[21] and Coats with Redfern[22] were used for kinetic parameters determination.

RESULTS AND DISCUSSION

Thermal analysis is a group of techniques in which a physical property of a substance and its reaction products is measured as a function of temperature while the substance is subjected to a controlled temperature program.

Thermal analysis techniques are widely used in the pharmaceutical sciences for the characterization and quality control of drugs, stability, drug-excipient interactions and purity studies of raw materials and pharmaceutical products[23,24].

Therefore the aim of this work was to apply different thermal analysis techniques for determination of related important information about the physical properties of OXY, (stability, compatibility, kinetic analysis) and to measure the kinetic parameters (activation energy, frequency factor and reaction order) according to the progress of reactions.

The TG/DTG curves (Figure 2) of OXY show that the drug is thermally decomposed in four steps. The first step occurs in the temperature range of 62.05-166.70 ºC with the loss of 10.66% which may be due to the loss of HCl molecule. The second step occurs at 166.70-354.91 ºC with about 46.18% weight loss which may be attributed to the loss of ($C_7H_{14}N_2O_2$) molecule. The third step occurs at 354.91-455.52 ºC with an estimated weight loss of 21.43 % which may be attributed to the loss of C_4H_9O molecule. The fourth step at 455.52–489.05 ºC with an estimated weight loss of 26.93% which may be attributed to the loss of C_6H_5O molecule. The weight losses appeared in DTA as endothermic and exothermic peaks which refer to several chemical processes occuring as a result of thermal degradation of the used drug at the temperature ranges were given in TABLE 1.

The DTA curve (Figure 3) exhibits endothermic peaks. The first endothermic peak at 161.95°C is due to the melting of the compound (reported melting point range in Clarke[25] is 157-160 °C). The sharp endothermic peak at 278.70°C is attributed to the first decomposition corresponding to the first mass loss observed in TG/DTG thermogram curves. The broad endothermic peaks at 488.77 °C are due to the pyrolysis

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TABLE 2 : Kinetic parameters for oxybuprocaine hydrochloride

Kinetic equation	Temperature range °C	Ea (KJ mol^{-1})	A	(S^{-1})	n	r
Arrhenius [22]	166.70-354.91	129.46	$1.32X10^{11}$		1	0.9849
Horowitz and Metzger [23]		106.16	$4.07 x10^{9}$		1	0.9752
Coats and Redfern [24]		143.65	$5.08 x10^{12}$		1	0.9597

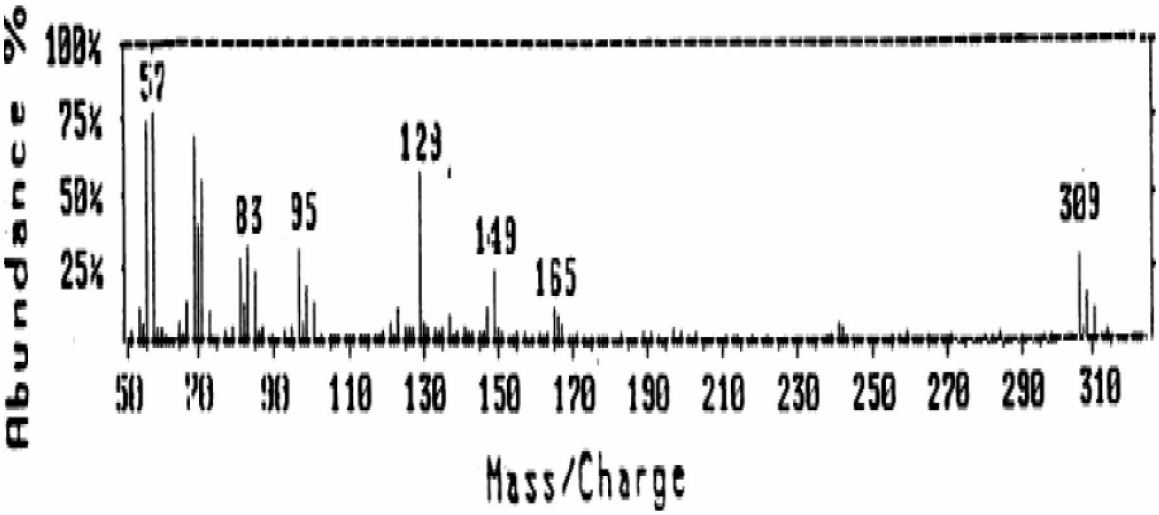

Figure 4 : The mass spectrum of oxybuprocaine hydrochloride.

of the compound.

The mass spectrum of oxybuprocaine hydrochloride is presented in Figure (4). Oxybuprocaine hydrochloride decomposes to give fragments, with m/z = 57 representing the butyl group ($C_4H_9^+$), m/z = 93 representing ($C_6H_5O^-$) group, m/z = 149 representing ($C_{10}H_{14}O^-$) group, m/z =165 representing ($C_{10}H_{14}O_2^-$) group and m/z = 309 representing ($C_{17}H_{28}N_2O_3$) group. The suggested thermal decomposition pathway of oxybuprocaine hydrochloride (Figure 5) was matched with the results obtained by mass spectroscopy.

Thermodynamic parameters such as activation energy (Ea), enthalpy (ΔH), entropy (ΔS) and Gibbs free energy change of the decomposition (ΔG) were obtained by using Arrhenius[22], Horowitz-Metzger[21] and Coats- Redfern[22] equations.

The results are shown in TABLE 2. The kinetic parameters obtained for the first step were: activation energy (Ea), Arrhenius constant (A), and reaction order (n). Calculated data from both methods evidenced also a first order kinetics behavior for oxybuprocaine hydrochloride.

Application of differential scanning calorimetry for purity determination of oxybuprocaine hydrochloride

The determination of purity is based on the assumption that impurities will depress the melting point of a pure material whose melting is characterized by a melting point (T_o) and an enthalpy of fusion (ΔHf). The melting transitions of a pure 100% crystalline material should be infinitely sharp, but impurities or defects in the crystal structure will broaden the melting range and lower the final melting point to a temperature lower than (T_o)[26]. The effect of impurities on (T_o) of oxybuprocaine hydrochloride was determined by DSC method based on Van't Hoff equation[27]:

The DSC curves (Figures 6-7) allowed determination of the melting points and the degrees of purity of OXY in raw material and pharmaceutical dosage form. The results obtained by the official method afforded values similar to those found by DSC (TABLE 3) Comparison of the data on the studied drugs revealed the importance of the DSC technique for quality control of bioactive drugs. The melting points obtained by DSC revealed the precision of the technique in yielding these thermal parameters. This justifies the use of DSC as a routine technique for identification of drugs designed for pharmaceutical use, through the melting point.

Application of thermal analysis to quality control of oxybuprocaine hydrochloride

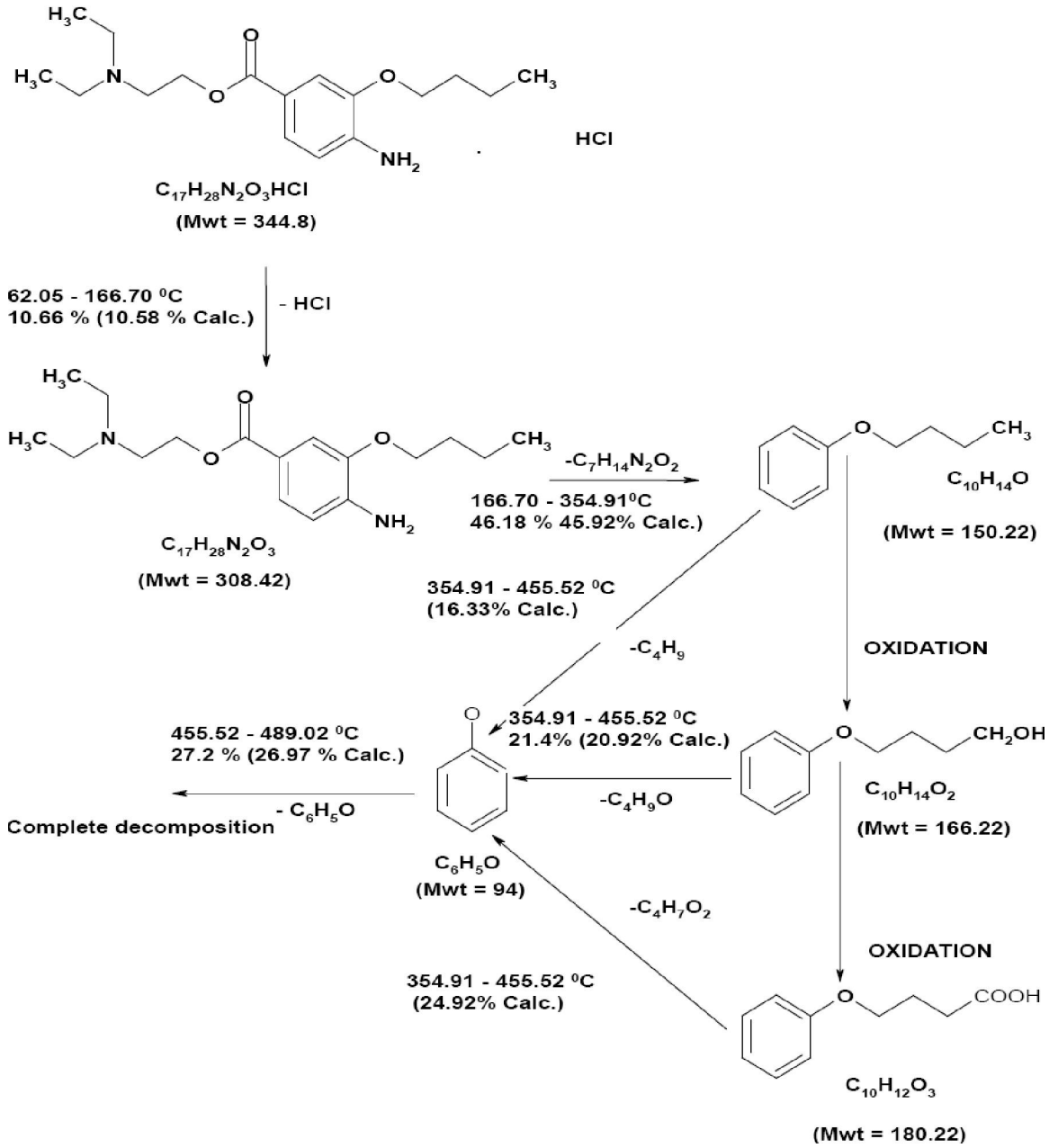

Figure 5 : The suggested thermal degradation of oxybuprocaine hydrochloride.

Thermal analysis is used as alternative technique for the determination of different quality parameters such as water content and ash content. No significant difference was observed between the obtained results when compared with official method as shown in TABLE 4.

Application of thermal analysis on benox® eye drops using differential scanning calorimetry

DSC curve of oxybuprocaine in drug product were presented in Figures (7) DSC curve of oxybuprocaine in drug substance exhibited one endothermic peak at 160.15 corresponding to the melting point of the pure drug. DSC curve of oxybuprocaine in drug product showing endothermic peak at 156.5 corresponding to the melting point of the pure drug so no interference between the drug and excipient TABLE 5. This was attributed to drug dissolution in the melted excipient (melting point of benzalkonium chloride 29-34°C & sodium chloride 801-804ºC). Unfortunately, the results obtained could not be compared with the reported method of Zheng et al [19] for the determination of the purity of OXY, since the journal was not available in

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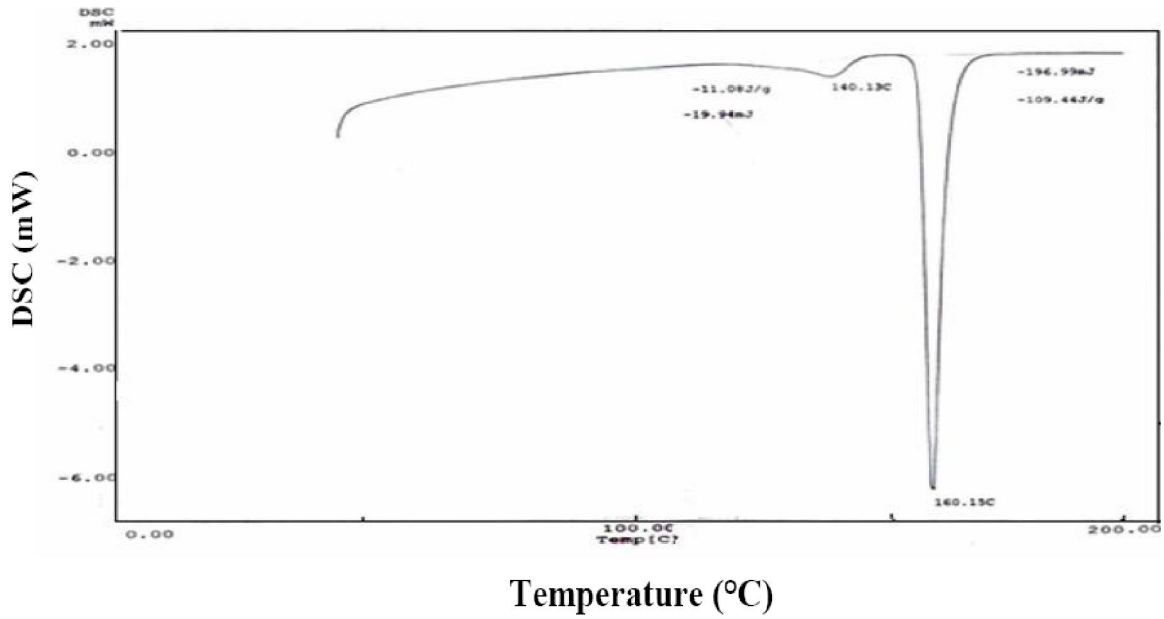

Figure 6 : DSC curve of oxybuprocaine hydrochloride.

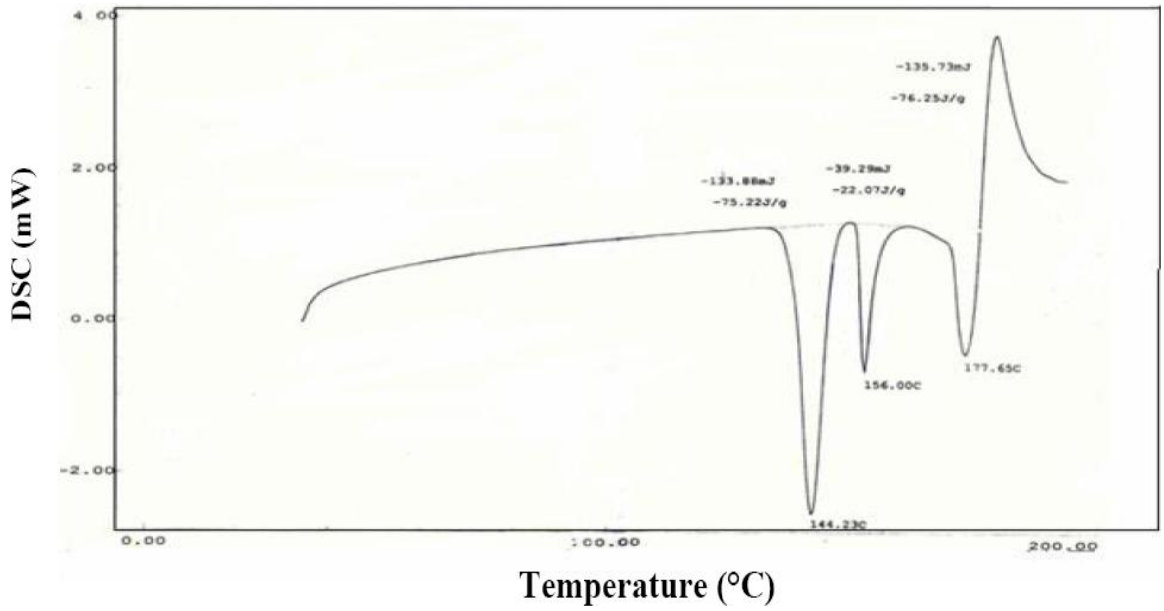

Figure 7 : DSC curve of oxybuprocaine hydrochloride in benox® eye drop.

TABLE 3 : Degree of purity and melting point of oxybuprocaine hydrochloride by DSC, melting point apparatus and official method[20]

Degree of purity%		Melting point °C			
DSC	official method[20]	DTA	DSC	Melting point apparatus	official method [20]
99.36	99.79	161.9	160.15	159	157 - 160

TABLE 4 : Quality control parameters obtained from the thermal analysis of oxybuprocaine hydrochloride

Water content %		Ash content %	
Thermal analysis method	Official Method[20]	Thermal analysis method	Official Method[20]
0	0.20% Max (1%)	0	0.01 Max (0.2%)

TABLE 5 : Application of the proposed DSC method for determination of the claimed amount of oxybuprocaine hydrochloride in pharmaceutical formulation

Dosage forms	Claimed amount% by the proposed DSC method	Claimed amount % by official method [20]
Benox® eye drops (0.4%oxybuprocaine HCl)	100.08	100.03

most scientific databases (science direct, Medline ……etc) and also the reported language is Chinese.

CONCLUSIONS

The thermal stability of oxybuprocaine HCl using different thermal techniques (TG/DTG, DTA, and DSC), was studied. The kinetic studies of oxybuprocaine HCl showed a thermal behavior characteristic to first order according to Ea. The correlation between mass spectra and thermal behavior of oxybuprocaine was studied. The data revealed correlation between the two techniques. The DSC data showed incompatibility between the studied drug and excipients. DSC provides a rapid method for purity determination attending a value between 98.5–101.5%, which is in agreement with the official method[20]. The simplicity, speed and low operational costs of thermal analysis of pharmaceuticals, justify its application in quality control. The results obtained are useful for the identification of these compounds and permitted interpretations concerning their thermal decomposition. Thermal stability of pharmaceutical compounds can be studied and compared by using thermal analysis techniques.

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