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ORIGINAL ARTICLE

Thermal analysis study of antihypertensive drug doxazosin mesilate

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Abstract Thermogravimetry and differential scanning calorimetry (DSC) are useful techniques that have been successfully applied in the pharmaceutical industry to reveal important information regarding the physicochemical properties of drug and excipient molecules such as stability, purity and formulation compatibility among others. The present work reports studies of the thermal behavior of antihypertensive drug doxazosin mesilate as raw material and in the form of tablets. The purity was determined by DSC and specialized pharmacopeial method. Analysis of the DSC data indicated that the degree of purity of doxazosin mesilate was similar to that found by the official HPLC method used in the British pharmacopoeia, BP 2011. The simplicity and sensitivity of thermal analysis justify its application in the quality control of pharmaceutical compounds.
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1. Introduction

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 improvement of the final product and for the determination of drug quality via the technological parameters. Differential scanning calorimetry (DSC) can be used in the pharmaceutical industry as an analytical tool of great importance for the identification and purity testing of active drugs, yielding results rapidly and efficiently. DSC has been applied for the quality control of raw materials used in pharmaceutical products. Several reports in the literature demonstrate the importance of thermal analysis by thermal gravimetric analysis (TGA), derivative thermogravimetry (DTG), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) in the characterization, polymorphism identification, and purity evaluation of drugs (Caira et al., 2004; Craig and Reading, 2007; El-Ries et al., 2011; Freitas et al., 2007; Gabbott, 2008; Macedo et al., 2002; Oliveira et al., 2005; Radha et al., 2010; Stulzer et al., 2008; Wassel, 2011; El-Ries et al., 2010; Attia et al., 2012).

Doxazosin mesilate (Fig. 1) is an alpha$_1$-adrenoceptor blocker with actions and uses similar to those of prazosin, but a longer duration of action. It is used in the management of hypertension and in benign prostatic hyperplasia to relieve symptoms of urinary obstruction (Sweetman, 2009).

Several methods have been reported on the determination of doxazosin mesilate, including the use of HPLC for its determination in the plasma and pharmaceutical formulations

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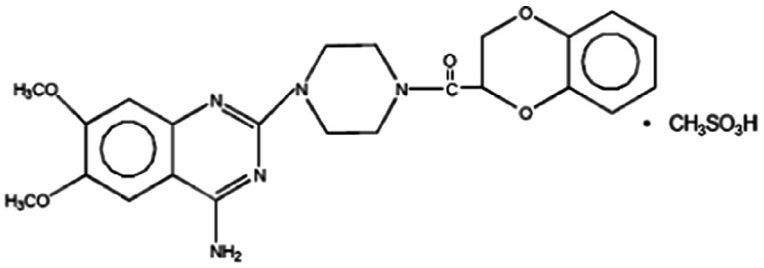

Figure 1 Chemical structure of doxazosin mesilate.

(Ojha et al., 2003; Jckman et al., 1991; Owens et al., 1997; Liu et al., 2010), differential pulse polarography (Ozgur et al., 1997; Altiokkia and Tuncel, 1998), cathodic stripping voltametry (Arranz et al., 1997), adsorptive stripping voltametry (De Betono et al., 1996) and stability indicating methods (Bebawy et al., 2002).

2. Experimental

2.1. Materials

Doxazosin mesilate, raw material and Doxacor tablets were provided from the Minapharm Pharmaceuticals and Chemical Industries, Cairo, Egypt. The purity of doxazosin mesilate was found to be 99.80% according to the British pharmacopoeia, BP 2011.

2.2. Methods

Thermal analysis studies were made by using simultaneous TGA–DTA thermal analyzer apparatus (Shimadzu DTG-60H). The experiments were performed between ambient and 800 °C. The temperature program had a heating rate of 10 °C/min. Dry nitrogen at a low rate of 30 ml/min was used as the purge gas. α-Al_2O_3 was used as the reference material.

DSC curves were measured on Shimadzu DSC-50 cell. Approximately 2 mg of samples was massed out and placed in a sealed aluminum pan. An empty aluminum pan was used as a reference. The purity determination was performed using a heating rate of 10 °C/min in the temperature range of 25–400 °C in nitrogen atmosphere with a flow rate of 30 ml/min. DSC equipment was preliminary calibrated with a standard of indium.

3. Results and discussion

3.1. Thermal analysis behavior of doxazosin mesilate

Fig. 2 indicates that the thermal decomposition of doxazosin mesilate occurs in three consecutive steps. The first step shows the loss of 28.31% in the temperature range of 240–365 °C due to the elimination of the substituent groups dimethoxy and methanesulfonate groups, the second step shows the loss of 24.78% in the temperature range of 365–457 °C due to the elimination of the $C_8H_7O_2$ molecule, the third step shows the loss of 46.54% in the temperature range of 457–800 °C due to the elimination of $C_{13}H_{12}N_5O$ group and the complete decomposition of the compound.

The DTA curve in Fig. 2 shows that the doxazosin mesilate has an endothermic peak and three exothermic peaks. The endothermic reaction peak which is not accompanied by weight loss occurs at 273 °C. This reaction may be attributed to the melting of the compound. Three exothermic peaks; an exothermic peak with its maximum at 325 °C may be attributed to the loss of dimethoxy and methanesulfonate groups, an exothermic peak at 455 °C as a shoulder may be attributed to loss of $C_8H_7O_2$ molecule and strong exothermic peak at 488 °C which may be attributed to loss of $C_{13}H_{12}N_5O$ and complete decomposition of the compound.

3.2. Determination of purity of doxazosin mesilate

An important concern of analytical chemistry is the determination of purity of organic compounds. Most techniques that are currently being employed in instrumental analysis involve the analysis of a given sample in comparison with a standard sample. Advances in analytical instrumentation require an extremely high degree of purity warranty for standard samples, the determination of purity is thus important not only for laboratory use, but also for a broad spectrum of applications in which the quality warranty of reagent and drugs is vitally important. There is an increasing need for more accurate determination methods that are easy to use.

Thermal methods are easy to use, can be performed quickly and are effective in measuring unknown impurities. On the other hand, DSC may be a simple and rapid method of estimating the purity of materials. However, its use has been limited to a substance of rather high purity. The minimum purity required for this method is approximately 98%. Therefore, the DSC method is rarely used by itself to warrant purity. For this reason, traditionally chromatographic techniques such as HPLC and GC are used for purity measurement (Mathkar et al., 2009).

The determination of purity is based on the assumption that impurities lower the melting point of a pure substance. The melting transition of a pure, 100% crystalline substance should be infinitely sharp, but impurities or defects in the crystal structure will broaden the melting range and lower the melting point (Hatakeyama and Liu, 1998). In a system which contains impurities, Van't Hoff equation approximately holds and allows the purity value to be calculated as follows:

$$T_f = T_0 - [(RT_0^2\ X/\Delta H_f).\ 1/F]$$

where T_f is the melting temperature of the sample, T_0 is the melting point of pure substance in Kelvin (K), R is the gas constant, ΔH_f is the heat of fusion, F is the fraction melted and X is the mole fraction of impurities.

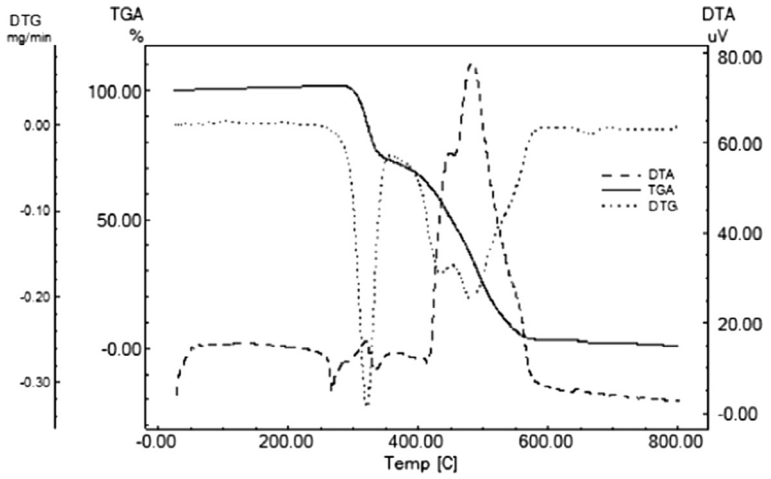

Figure 2 TGA, DTG and DTA curves of doxazosin mesilate.

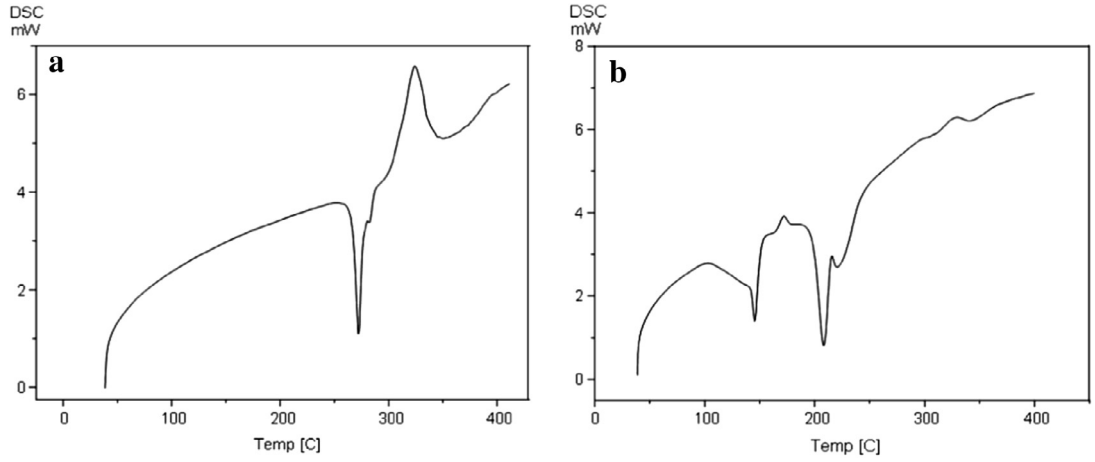

Figure 3 DSC curves of doxazosin mesilate (a) and doxacor tablets (b).

Fig. 3 shows the DSC curve for doxazosin mesilate indicating an endothermic reaction with a sharp peak at 275 °C related to the melting point of the drug and another exothermic peak at 325 °C. The sample seems to be suitable for purity determination by the DSC method, the drug was found to be very pure (99.97%). As shown in Table 1 the purity of the drug was compared with that obtained by using the official method (99.80%) confirming low impurity content and also Table 1 showed satisfactory results for the melting point of the used drug by using different methods.

3.3. Quality control application of doxazosin mesilate

Thermal analysis is used as an alternative technique for the determination of different quality parameters such as water

Table 1 Melting point and degree of purity of doxazosin mesilate.

Melting point (°C)				Degree of purity (%)	
DTA method	Melting point apparatus[a]	DSC method	Literature[b]	DSC method	Official method[c]
273	276	275	275–277	99.97%	99.80%

[a] Mettler FP 80.
[b] Clark's analysis of drugs and poisons (Anthony et al., 2004).
[c] British pharmacopoeia (2011).

Table 2 Quality control parameters obtained from the thermal analysis of doxazosin mesilate compared with reported method.

Water content (%)		Ash content (%)	
Thermal analysis method	Reported method[a]	Thermal analysis method	Reported method[a]
0.38	0.65 (Max. 1.5%)	Zero	0.05 (Max. 0.1%)

[a] British pharmacopoeia (2011).

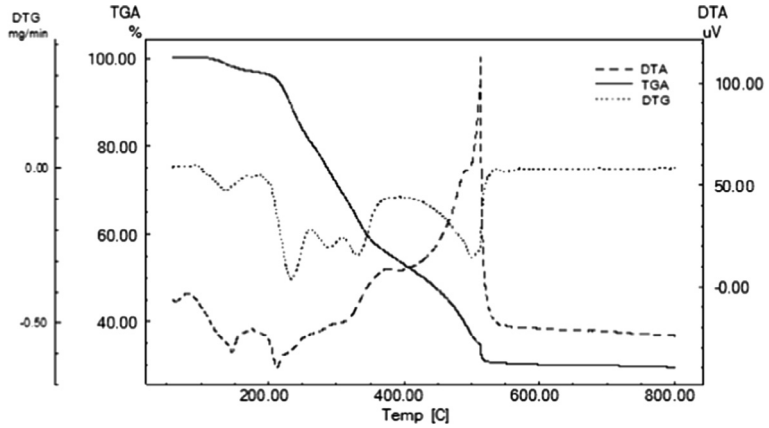

Figure 4 TGA, DTG and DTA curves of doxacor tablets.

content and ash content. No significant difference was observed between the obtained results when compared with the reported method as shown in Table 2.

3.4. Thermal analysis application of doxacor tablets

TGA, DTG and DTA of doxacor tablets curves were presented in Fig. 4. The DTA of doxacor tablets indicates the melting of doxazosin mesilate at 212 °C. It was observed that the drug melting event occurs with mass loss; the onset and the end set temperatures of the DTA curve of the doxacor tablets were shifted to lower temperatures than that of the DTA curve of doxazosin mesilate. In fact a similar effect was observed for other drug excipients mixtures and was attributed to drug dissolution in the melted excipients (Cides et al., 2006).

Fig. 5 shows the DTA curves of these excipients and doxacor tablets. The excipients can produce a different environment in which the behavior of the drug is modified but they are still compatible with the drug. Based on the results of DTA curves, majority of the excipients such as Mg stearate, povidone and microcrystalline cellulose were found to be compatible with the drug.

DSC curve of doxacor tablets (Fig. 3) shows a sharp endothermic peak at 208.22 °C corresponding to the melting point of doxazosin mesilate. By comparing the melting point values of the pure drug shown in Table 1 with those obtained for doxazosin mesilate in doxacor tablets we found that the melting point values of the pure drug are higher than those in tablets due to the presence of excipients.

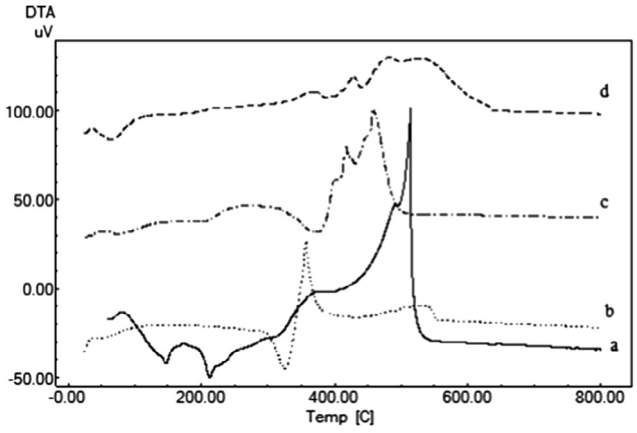

Figure 5 DTA curves of doxacor tablets (a), microcrystalline cellulose (b), magnesium stearate (c) and povidone (d).

4. Conclusion

Solid state reactions include phase transitions such as melting, evaporation and sublimation, as well as decomposition reactions resulting in the production of different compounds. Thermal analysis can be used to monitor these reactions by determining the rate of mass loss as the sample undergoes the process. Thermal analysis methods are widely used in all fields of pharmaceutical sciences but especially in pre-formulation studies. These techniques are unique for the characterization of compounds and mixtures. The excipients can produce a different environment in which the behavior of the drug is modified but they are still compatible with the drug. Thermal analysis can be used in quality control of pharmaceutical compounds. DSC data indicated that the degree of purity of doxazosin mesilate is similar to that found by the official method.

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