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Research Article

THERMOANALYTICAL STUDY OF ALFUZOSIN HCL

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ABSTRACT

Thermal analysis (TGA, DTG and DTA) and differential scanning calorimetry (DSC) have been used to study the thermal behavior of alfuzosin HCl as a raw material and in tablets. Thermogravimetric analysis (TGA/DTG), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) were used to determine the thermal behavior and purity of the used drug. Thermodynamic parameters such as activation energy (E*), enthalpy (ΔH*), entropy (ΔS*) and Gibbs free energy change of the decomposition (ΔG*) were calculated using different kinetic models. The purity value for the drug was found to be 99.99%. Thermal analysis technique gave satisfactory results to obtain quality control parameters such as melting point, water content and ash content in comparison to what were 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 data indicated that the degree of purity of Alfuzosin HCl is similar to that found by official methods.

Keywords: Alfuzosin HCl, TGA, DTG, DTA, DSC, Xatral tablet, Quality control.

INTRODUCTION

Alfuzosin HCl (Fig. 1) is a quinazoline derivative that reduces the tone of the contractions of the prostate, bladder base and proximal urethral smooth muscle, acting as a selective and competitive antagonist of α1-adrenoceptors.[1,2] It is regarded as first line therapy for symptomatic treatment of non-complicated mild to moderate benign prostatic hyperplasia, because it provides rapid and sustained symptom relief irrespective of prostate size.[3-6] Recent studies indicate that alfuzosin is also a drug of choice for urinary bladder dysfunction in patients with nephrotuberculosis.[7, 8]

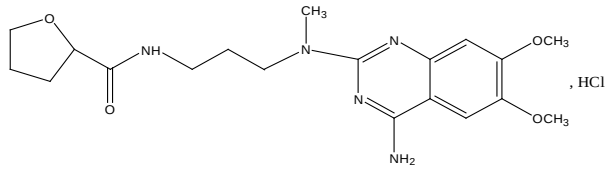

Fig. 1: Chemical structure of Alfuzosin HCl

Thermal analysis techniques that deliver extremely sensitive measurement of heat change can be applied on a broad scale with pharmaceutical development. The increasing use of the combined techniques is providing more specific information, and thus this facilitates more rapid interpretation of the experimental curves obtained.[9] The need to measure a range of physical parameters has led to the development of numerous techniques such as thermogravimety (TGA), derivative thermogravimetry (DTG) differential thermal analysis (DTA) and differential scanning calorimetry (DSC). In pharmaceutical sciences thermal methods of analysis have found important applications, these techniques are widely used in pharmaceutical sciences for the characterization of solid drugs and excipients. Also these techniques are established for quality control, stability, drug-excipients interaction, polymorphism and purity studies of raw materials and pharmaceutical products.[10, 21]

In the present work, thermal behavior of alfuzosin HCl was studied by using different techniques such as TGA, DTG, DTA and DSC.

MATERIALS AND METHODS

Materials

Alfuzosin HCl, raw material and Xatral tablets were provided from Amriya for Pharmaceutical Industries, Alexandria, Egypt.

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 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.

Thermodynamic parameters such as activation energy (E*), enthalpy (ΔH*), entropy (ΔS*) and Gibbs free energy change of the decomposition (ΔG*) were obtained by using the Horowitz-Metzger and Coats-Redfern relations.[22, 23]

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

RESULTS AND DISCUSSION

The TGA-DTG curves in Fig. 2 show that the thermal decomposition of Alfuzosin HCl occurs in three consecutive steps. The first step occurs in the temperature range of 190-286 °C with the loss of 8.60% due to loss of HCl molecule, the second step occurs in the temperature range of 286-475 °C with the loss of 43.44% due to loss of $C_9H_{17}N_2O_2$ molecule. The last step occurs with the loss of 48.65% in the temperature range of 475-800 °C due to loss of $C_{10}H_{10}N_3O_2$ molecule.

The DTA curve of Alfuzosin HCl in Fig. 2 shows two peaks (endothermic and exothermic peaks). The endothermic reaction which is accompanied by the loss of HCl molecule; the reaction has its maximum at 237 °C. This reaction may be attributed to the melting of the compound. The exothermic peak at 552 °C may be attributed to the pyrolysis of the compound.

Both Horowitz-Metzger (HM) and Coats-Redfern (CR) methods were applied for calculating the different thermodynamic parameters of the thermal decomposition steps of Alfuzosin HCl. The results were listed in Table 1.

Determination of purity

An important concern of analytical chemistry is the determination of purity of organic compounds, most techniques that are currently used such as chromatographic techniques involves the analysis of a given sample in comparison with a standard samples.

The determination of purity using DSC method is based on the assumption that the impurities will 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.[24] In a system which contains impurities, Van't Hoff equation approximately holds and allows the purity value to be calculated as follow:

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

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 mole fraction of impurities.

The DSC curve of Alfuzosin HCl in Fig. 3 shows an endothermic reaction with a very sharp peak at 235 °C due to melting of the drug and another weak exothermic peak at 320 °C. The sample seems to be suitable for purity determination by the DSC method. The drug was found to be very pure 99.99%, the purity of the drug was compared with that obtained by using the official method 99.70% confirming low impurities content. The results were listed in Table 2.

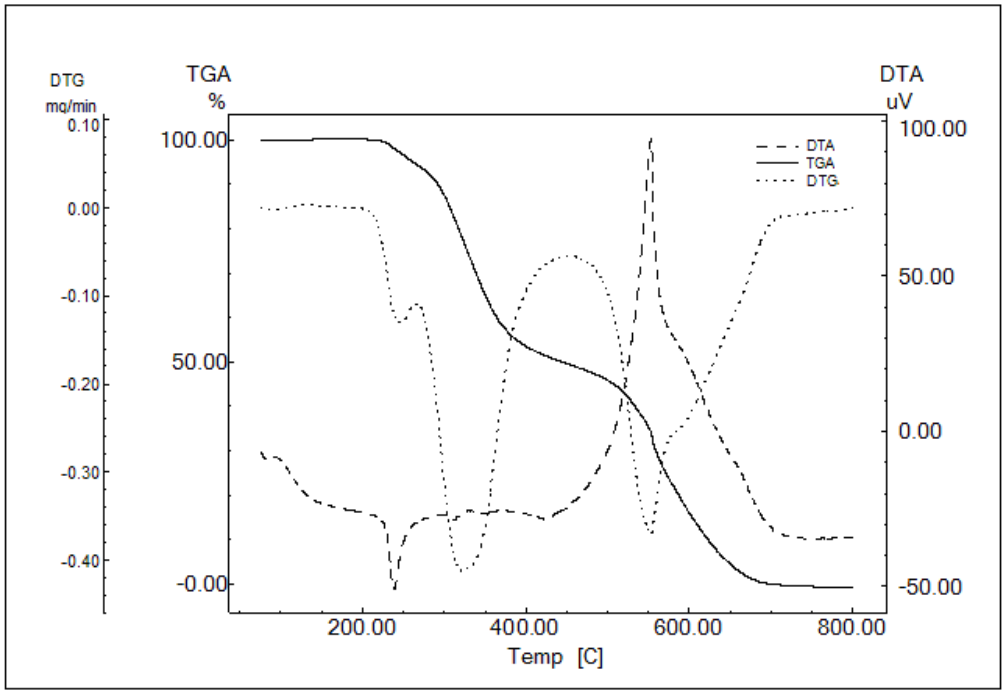

Fig. 2: TGA, DTG and DTA curves of Alfuzosin HCl

Table 1: Thermodynamic parameters of the thermal decomposition of Alfuzosin HCl

Temperature range (°C)	E* (kJ/mol) HM (CR)	A (S^{-1}) HM (CR)	ΔS* (kJ/mol. K) HM (CR)	ΔH* (kJ/mol) HM (CR)	ΔG* (kJ/mol) HM (CR)
190-286	97.63 (94.98)	2.92×10^9 (2.25×10^8)	-68.32 (-89.63)	93.31 (90.67)	128.27 (137.18)
286-475	76.07 (67.27)	1.04×10^6 (4.12×10^4)	-135.60 (-162.41)	71.08 (62.27)	152.57 (159.89)
475-800	61.25 (55.85)	8.18×10^2 (1.61×10^2)	-197.65 (-211.16)	54.39 (48.99)	217.45 (223.20)

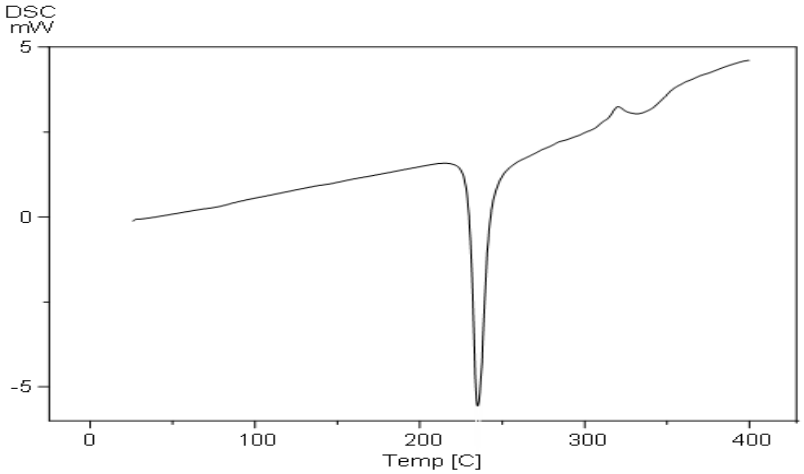

Fig. 3: DSC curve of Alfuzosin HCl

Table 2: Melting point and degree of purity of Alfuzosin HCl

Melting point (°C)				Degree of purity (%)	
DTA method	**Melting point apparatus**	**DSC Method**	**Literature[25]**	**DSC Method**	**Official Method[26]**
237	233	235	235	99.99%	99.70%

Application of thermal analysis to quality control of Alfuzosin HCl

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 reported method as shown in Table 3.

Application of thermal analysis on Xatral tablets

Figure 4 shows the TGA, DTG and DTA curves of Xatral tablets. The DTA curves of Alfuzosin HCl and its tablets were showed in Fig. 5, where, the onset and the end set temperatures were shifted to lower temperature. The DTA curve of Xatral tablets indicates that the melting point of Alfuzosin HCl is 186 °C. It was observed that the drug melting event occurs with mass loss, suggesting an interaction but not necessary corresponding to incompatibility. In fact a similar effect was observed for other drug excipients mixtures and was attributed to drug dissolution in the melted excipients.[27]

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, majority of the excipients (Mg stearate, povidone, microcrystalline cellulose) were found to be compatible with the drug. See Figures 6 and 7.

Table 3: Quality control parameters obtained from the thermal analysis of Alfuzosin HCl compared with reported method

Water content (%)		Ash content (%)	
Thermal analysis method	**Reported method[26]**	**Thermal analysis method**	**Reported method[26]**
0.025	0.15 (Max. 0.5%)	zero	0.01 (Max. 0.1%)

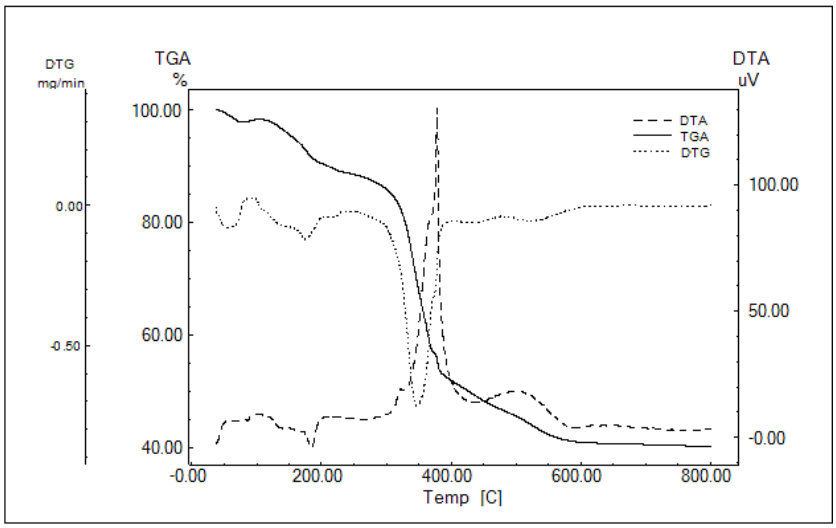

Fig. 4: TGA, DTG and DTA curves of Xatral tablets

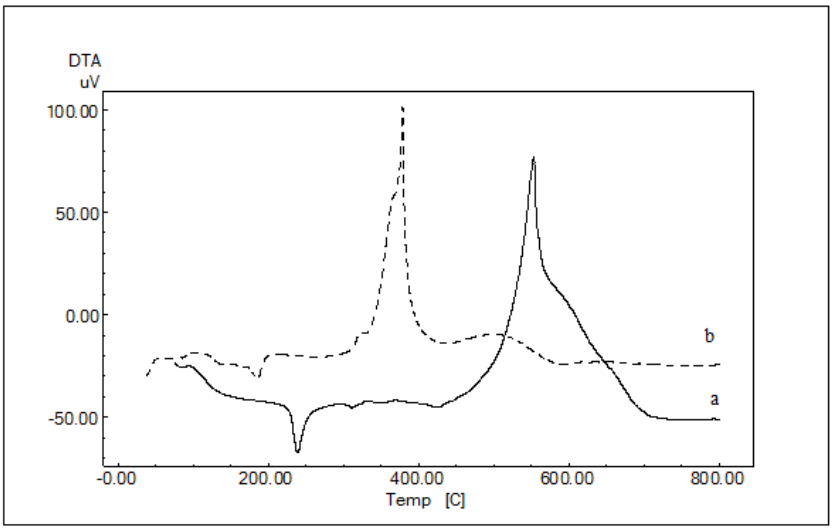

Fig. 5: DTA curves of Alfuzosin HCl (a) and Xatral tablets (b)

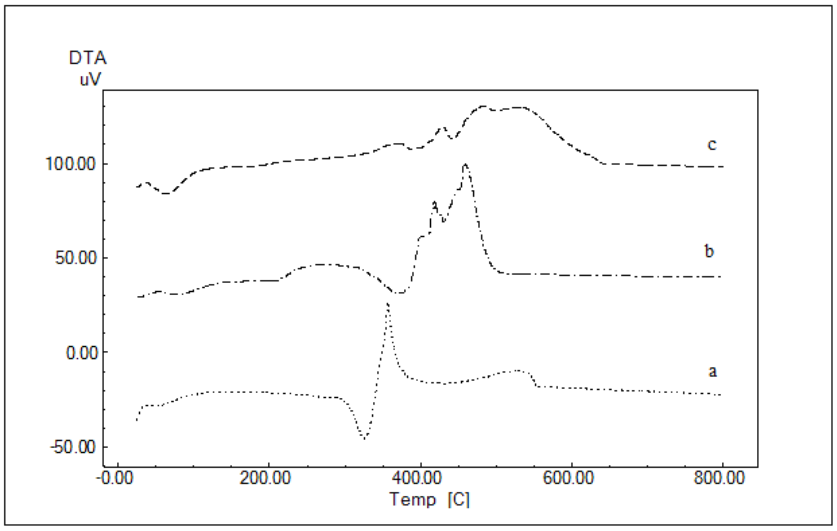

Fig. 6: Excipients microcrystalline cellulose (a), Magnesium stearate (b) and povidone (c)

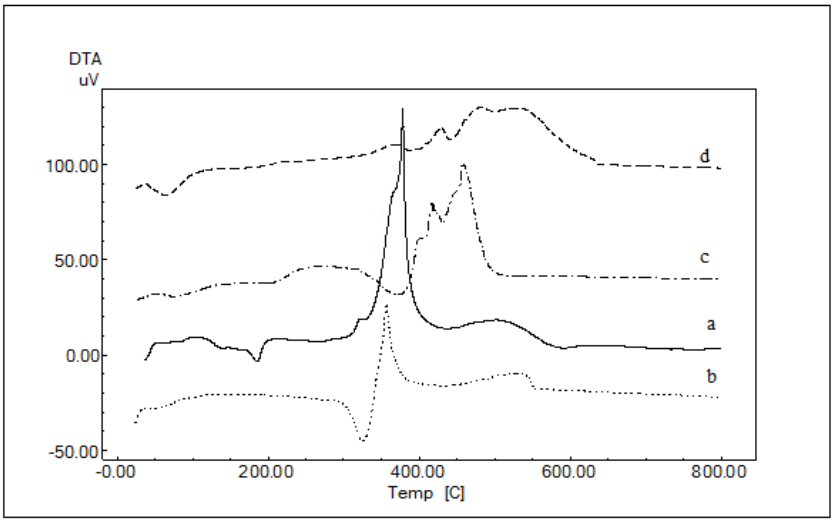

Fig. 7: DTA curves of Xatral tablets (a), microcrystalline cellulose (b), magnesium stearate (c) and povidone (d)

The DSC curve of Xatral tablets (Fig. 8) shows very sharp endothermic peak at 182.18 °C corresponding to melting point of Alfuzosin HCl. By comparing the melting point values for Alfuzosin HCl in tablets with those values obtained for the pure drug showed in Table 2, we found that the melting point values of the pure drug are higher than those in tablets which may be attributed to the presence of excipients.

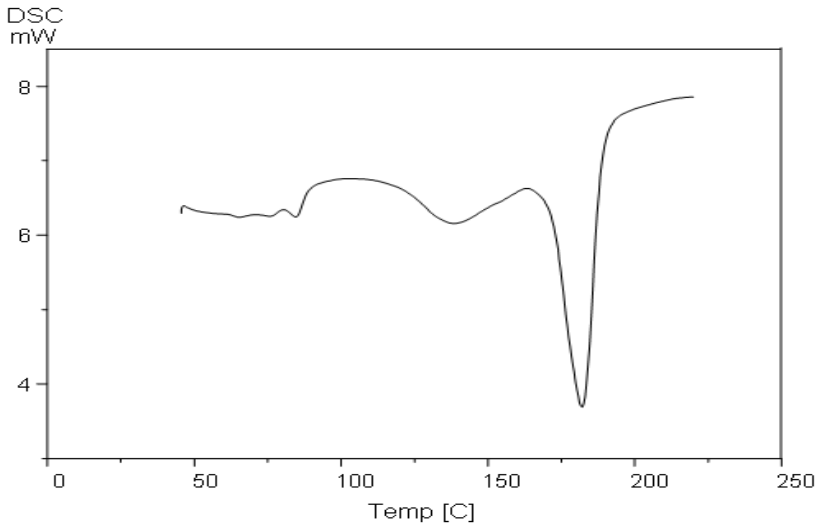

Fig. 8: DSC curve of Xatral tablet

CONCLUSION

Thermal analysis and differential scanning calorimetry (DSC) are the techniques used for the screening or testing of the compatibility of drug component with the excipients. Comparison of the data obtained in this work reveals the importance of the thermal analysis and DSC techniques for the quality control of bioactive drugs. The melting points obtained by DSC reveal the precision of the technique in yielding this thermal parameter. This justifies the use of DSC as a routine technique for the identification of compounds destined for pharmaceutical use through the melting point. The uses of clean, fast and simple techniques of the analytical methods applied to obtain the results are the reasons behind the even growing importance of thermal analysis in the quality control of active ingredients for medications.

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