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Thermoanalytical Investigation of Terazosin Hydrochloride

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ABSTRACT

Purpose: Thermal analysis (TGA, DTG and DTA) and differential scanning calorimetry (DSC) have been used to study the thermal behavior of terazosin hydrochloride (TER). ***Methods:*** 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. ***Results:*** The purity of the used drug was determined by differential scanning calorimetry (99.97%) and specialized official method (99.85%) indicating to satisfactory values of the degree of purity. Thermal analysis technique gave satisfactory results to obtain quality control parameters such as melting point (273 ºC), water content (7.49%) and ash content (zero) in comparison to what were obtained using official method: (272 ºC), (8.0%) and (0.02%) for melting point, water content and ash content, respectively. ***Conclusion:*** 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 terazosin hydrochloride is similar to that found by official method.

Introduction

Terazosin hydrochloride (TER) showed in Figure 1 is a α_1-adrenoceptor blocker with a long lasting action. α_1-adrenoceptor antagonists are clinically useful for the improvement of urinary obstruction due to benign prostatic hyperplasia (BPH), and their pharmacologic effect is mediated through the blockade of prostatic α_1-adrenoceptor.[1-3] It is used in the management of hypertension and in benign prostate hyperplasia to relieve symptoms of urinary obstruction. TER is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration and is extensively metabolized in the liver to yield piprazine and three other inactive metabolites. Absorption is not affected by the presence of food. The major route of elimination is via the biliary tract and the drug is excreted in faeces (60%) and urine (40%). 10% is excreted as the parent drug and the remainder as its metabolites. Renal impairment shows no significant effect on pharmacokinetics.[4]

TER could be determined by using several analytical techniques, potentiometry,[5] voltammetry,[6,7] spectrophotometry,[8,9] fluorimetry,[10,11] and HPLC.[12-14]

Thermal analysis including TGA, DTG, DTA and DSC are useful techniques that have been successfully applied in the pharmaceutical industry to reveal important information regarding the physicochemical properties of drug and excipients such as polymorphism, stability and purity.[15-21] DSC can be used 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.[22]

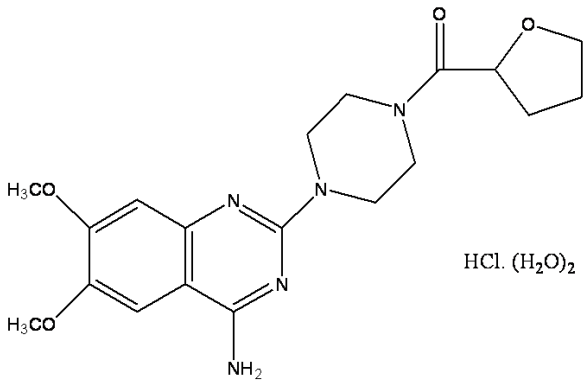

Figure 1. The molecular structure of TER

The present work represents the study of the thermal behavior of TER, in comparison with the methods employed for purity testing in the pharmaceutical industry in relation to the application of thermal techniques in the quality control of medications.

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Materials and Methods

Materials

Terazosin hydrochloride was provided from the reference standard department of NODCAR, which manufactured by Pharaonia Amriya for Pharmaceutical Company, Alexandria, Egypt. The purity of terazosin hydrochloride was found to be 99.85% and the impurities content was found to be 0.15% according to the potentiometric and liquid chromatographic methods which reported in the British pharmacopoeia, BP 2011.

Methods

The thermal analysis of TER was performed using Shimadzu thermogravimetric analyzer TGA-60H in a dynamic nitrogen atmosphere. Highly sintered α-Al_2O_3 was used as a reference. The mass losses of samples and heat response of the change of the sample were measured from room temperature up to 750 ºC. The heating rate was 10 ºC/min.

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 which applied for the first order kinetic process.[23,24]

Horowitz and Metzger Method [23]

The Horowitz-Metzger equation can be represented as follows:

$$\log .[\log \frac{W_f}{W_f - W}] = \frac{\theta . E^*}{2.303 R T_s^2} - \log 2.303$$

Where W_f was the mass loss at the completion of the decomposition reaction, W was the mass loss up to temperature T, R was the gas constant, T_s was the DTG peak temperature and θ = T-T_s. A plot of log [log W_f / (W_f - W)] against θ would give a straight line and E^* could be calculated from the slope.

Coats-Redfern Method [24]

The Coats-Redfern method equation can be represented as follows:

$$\log \left(\frac{\log \left[W_f / W_f - W \right]}{T^2} \right) = \log \left[\frac{AR}{\phi E^*} \left(1 - \frac{2RT}{E^*} \right) \right] - \frac{E^*}{2.303 RT}$$

Where ϕ was the heating rate. Since 1- 2RT / E^*≅1, the plot of the left-hand side of equation against 1/T would give a straight line. E^* was then calculated from the slope and the Arrhenius constant (A) was obtained from the intercept.

The entropy ΔS^*, enthalpy ΔH^*, and free energy ΔG^* of activation were calculated using the following equations:

$$\Delta S^* = 2.303 \, [\log (Ah / kT)] \, R$$
$$\Delta H^* = E^* - RT$$
$$\Delta G^* = H^* - T_s \Delta S^*$$

Where k and h were the Boltzman and Planck constants, respectively. So the calculated values of E^*, ΔS^*, ΔH^*, and ΔG^* could be obtained.

DSC curves were measured on Shimadzu DSC-50 cell. Approximately 2 mg of samples was weighed 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 ºC/min in the temperature range from 25 to 320 ºC in nitrogen atmosphere with flow rate of 30 ml/min. DSC equipment was calibrated with indium.

Results and Discussion

Thermal Analysis of TER

Thermal analysis data containing thermogravimetric analysis (TGA), Derivative thermal analysis (DTG) and Differential thermal analysis (DTA) curves of the drug are shown in Figure 2. Thermal degradation pattern of TER was shown in Figure 3. The weights losses, physical and chemical changes during thermal degradation of the drug are presented in Table 1.

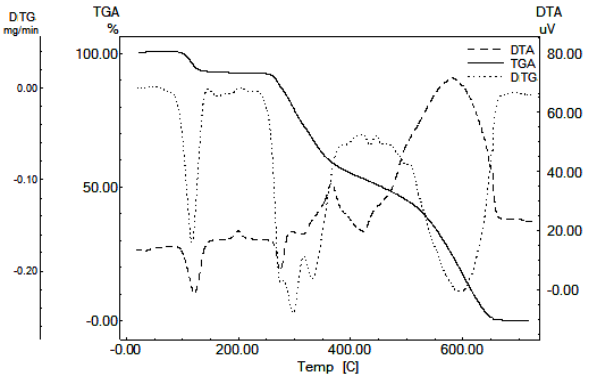

Figure 2. TGA, DTG and DTA curves of TER.

The TGA curve shows that TER is thermally decomposed in four steps. The first step occurs at 25-150 ºC as a result of 7.59% estimated weight loss which may be due to the loss of two crystal water molecules. The second step occurs at 150-280 ºC with about 7.71% weight loss which may be due to the loss of HCl molecule. The third step occurs in two stages at 280-320 ºC with an estimated weight loss of 14.98% which may be attributed to the loss of C_4H_7O molecule and at 320-341 ºC with an estimated weight loss of 6.18% which may be attributed to the loss of CO molecule. The fourth step occurs in two stages at 341-490 ºC with an estimated weight loss of 18.56% which may be attributed to the loss of $C_4H_8N_2$ molecule and at 490-700 ºC with an estimated weight loss of 45.31% which may be attributed to the loss of $C_{10}H_{10}N_3O_2$ molecule. The weight losses appeared in DTA as endothermic and exothermic peaks which refer to several chemical processes occur as a result of thermal degradation of the used drug at the temperature ranges were given in Table 1. These results indicate the compatibility between mass fragmentation and thermal degradation of the used drug.[4]

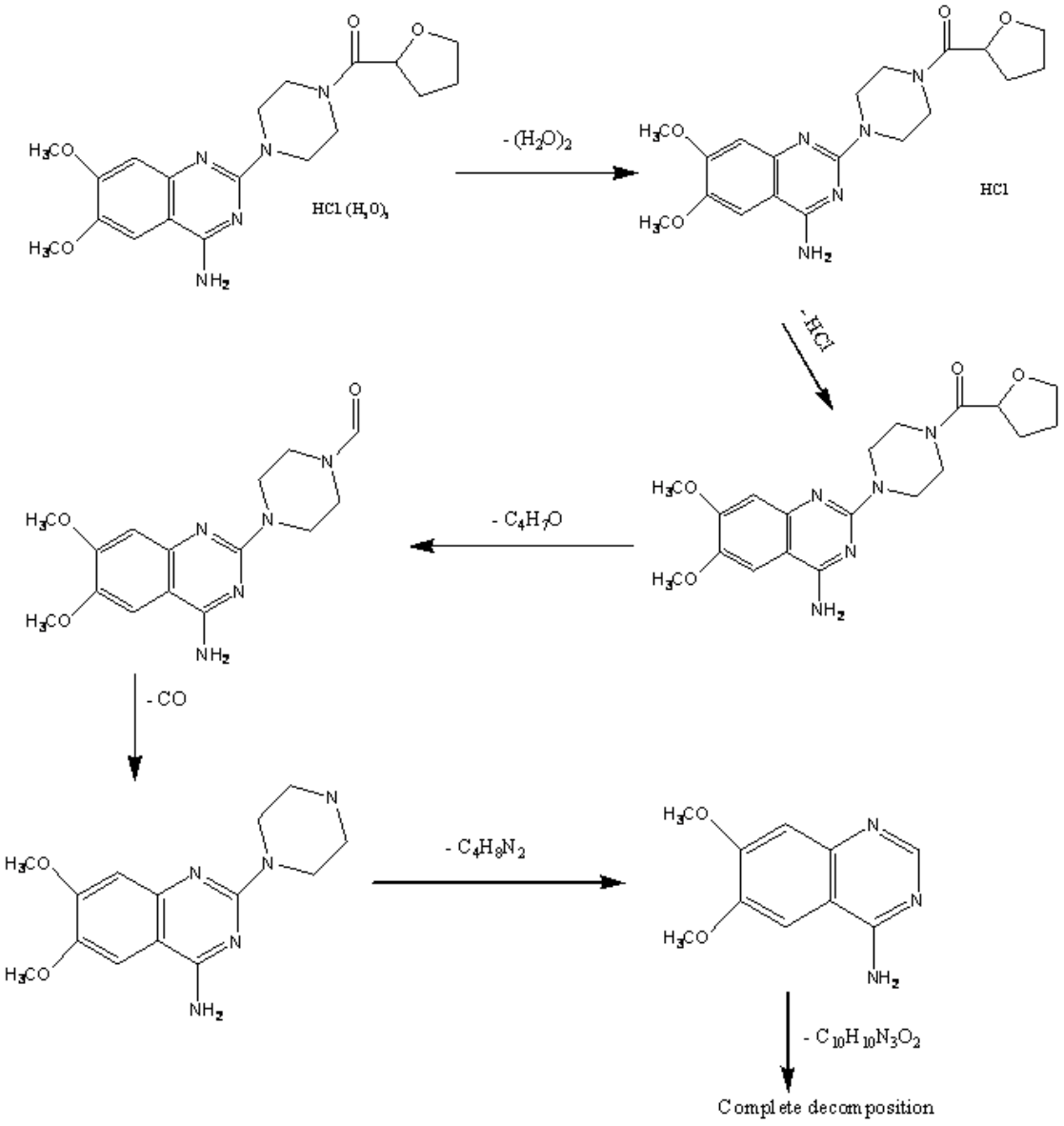

Figure 3. Thermal degradation pattern of TER.

Table 1. Thermogravimetric data (TGA, DTG and DTA) of TER.

Temperature range (°C)	DTG_{max} (°C)	Mass loss (%)	Assignment	DTA# (°C)
25-150	117	7.59	Loss of water molecules	119 (+)
150-280	275	7.71	Loss of HCl molecule and melting	199 (-), 273 (+)
280-320	296	14.98	Loss of C_4H_7O molecule	--------
320-341	332	6.18	Loss of CO molecule	--------
341-490	433	18.56	Loss of $C_4H_8N_2$ molecule	367 (-)
490-700	595	45.31	Loss of $C_{10}H_{10}N_3O_2$ molecule	578 (-)
# (+) = endothermic, (-) = exothermic				

Both Horowitz-Metzger (HM) and Coats-Redfern (CR) methods were applied for calculating the different thermodynamic parameters of the thermal decomposition steps of TER. The results were listed in Table 2.

Table 2. Thermodynamic parameters of the thermal decomposition of TER

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)
25-150	152.10 (131.47)	2.84×10^{17} (9.50×10^{16})	144.44 (77.88)	148.87 (128.23)	92.53 (97.85)
150-280	51.81 (53.42)	6.47×10^{-2} (2.41×10^{-3})	-272.78 (-300.15)	625.39 (782.71)	150.11 (165.26)
280-320	112.95 (104.70)	9.82×10^{9} (8.55×10^{8})	-59.01 (-79.31)	108.21 (99.96)	141.80 (145.09)
320-341	132.31 (121.38)	1.16×10^{11} (1.30×10^{10})	-39.02 (-57.20)	127.29 (116.34)	150.89 (150.95)
341-490	32.35 (18.80)	1.93×10 (1.14)	-227.49 (-251.05)	26.48 (12.93)	187.10 (190.17)
490-700	121.18 (99.67)	3.79×10^{6} (7.61×10^{4})	-127.87 (-160.37)	113.96 (92.45)	224.95 (231.65)

Determination of Purity of TER

DSC can be successfully used as a complementary or an alternative technique to verify purity of a compound provided that the material is at least 98% pure. Main advantages of purity analysis by DSC are minimal sample requirement and shorter analysis time as compared to chromatographic analysis.[25] Van't Hoff equation [$T_f = T_0 - [(R\ T_0^2\ X/\Delta H_f).\ 1/F]$] was used to determine the purity value, 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. 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.[26]

DSC thermogram of TER is shown in Figure 4. An endothermic reaction with a broad peak at 141 ºC, a weak exothermic peak at 199 ºC and an endothermic sharp peak at 274 ºC correspond to the loss of water molecules, the loss of HCl molecule and the drug melting, respectively. These results are in close agreement with that obtained from the DTA profile. Applying DSC method and Van't Hoff equation indicated that the sample is very pure (99.97%). This value was in close agreement with the results obtained by using the official method (99.85%) confirming low impurity content (Table 3).[27]

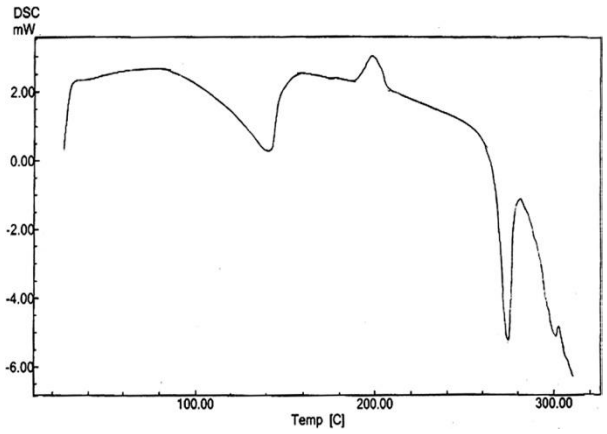

Figure 4. The DSC curve of TER.

Table 3. Melting point and degree of purity of TER.

Melting point (°C)				Degree of purity (%)	
DTA method	Melting point apparatus	DSC Method	Literature [4]	DSC Method	Official Method [27]
273	272	274	271-274	99.97%	99.85%

Thermal Analysis Application of TER

Different quality parameters such as water content and ash content were determined by using thermal analysis method. No significant difference was observed between the obtained results when compared with reported official method as shown in Table 4. [27]

Table 4. Quality control parameters obtained from the thermal analysis of TER compared with reported method

Water content (%)		Ash content (%)	
Thermal analysis method	Reported method [27]	Thermal analysis method	Reported method [27]
7.49	8.0 (7.0-8.6)	zero	0.02 (Max. 0.1%)

Conclusion

The comparison between mass fragmentation and thermal degradation of TER could show the agreement or the disagreement between the two techniques used in studying the drug fragmentation pathways. The obtained results indicate the compatibility between mass fragmentation and thermal degradation of TER. Therefore fragmentation pathway of TER was correctly determined. Thermal analysis methods are widely used in all fields of pharmaceutical sciences. These techniques are unique for the characterization of compounds and mixtures. Differential scanning calorimetry provides a satisfactory result for purity determination of the drug when compared with the official methods. Thermal analysis method might be a very useful tool to determine some quality control parameters such as water content and ash content comparing with results obtained by using the official methods.

Conflict of Interest

There is no conflict of interest in this study.

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