Advanced Pharmaceutical Bulletin, **2013**, 3(1), 147-152
doi: http://dx.doi.org/10.5681/apb.2013.025
http://apb.tbzmed.ac.ir/

Thermoanalytical Investigation of Terazosin Hydrochloride

Ali Kamal Attia*, Mona Mohamed Abdel-Moety

National Organization for Drug Control and Research, P.O. Box 29, Cairo, Egypt.

ARTICLEINFO

Article Type:
Research Article

Article History:
Received: 19 October 2012
Revised: 16 November 2012
Accepted: 18 November 2012
ePublished: 7 February 2013

Keywords:
Terazosin hydrochloride
Thermal analysis
Differential scanning calorimetry
Purity

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]

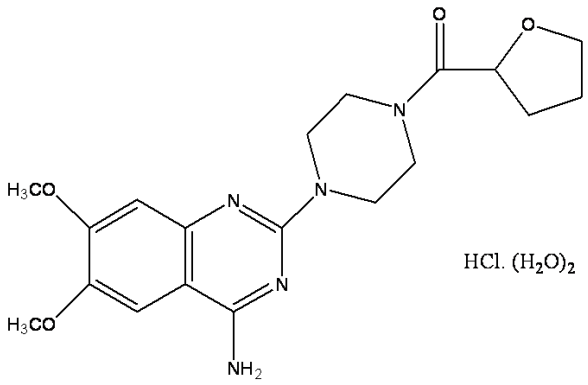

Figure 1. The molecular structure of TER

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.

***Corresponding author:** Ali Kamal Attia, National Organization for Drug Control and Research, P.O. Box 29, Cairo. Tel: +20-238702103, Fax: +20-235855582, Email: alikamal1978@hotmail.com

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 / $E^* \cong 1$, 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.

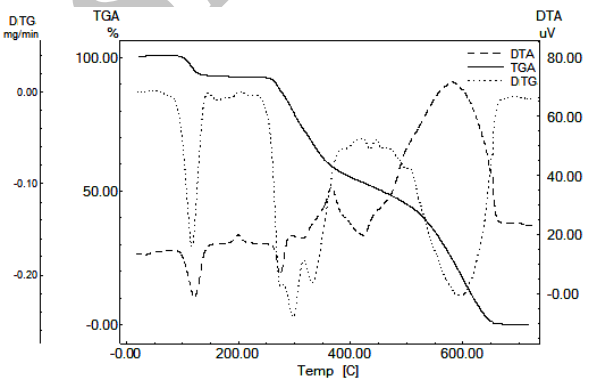

Figure 2. TGA, DTG and DTA curves of TER.

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]

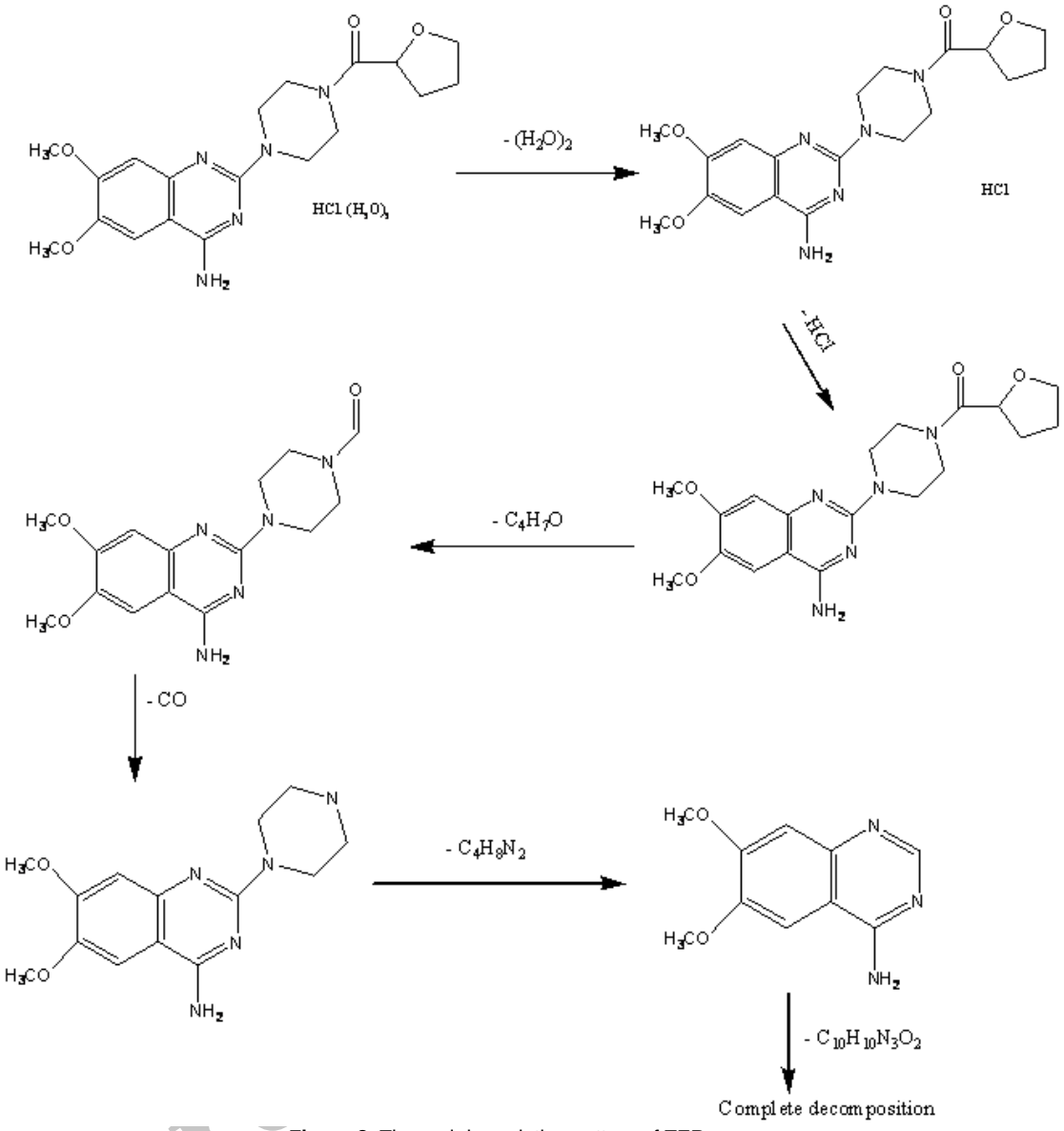

Figure 3. Thermal degradation pattern of TER.

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 °C, a weak exothermic peak at 199 °C and an endothermic sharp peak at 274 °C 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]

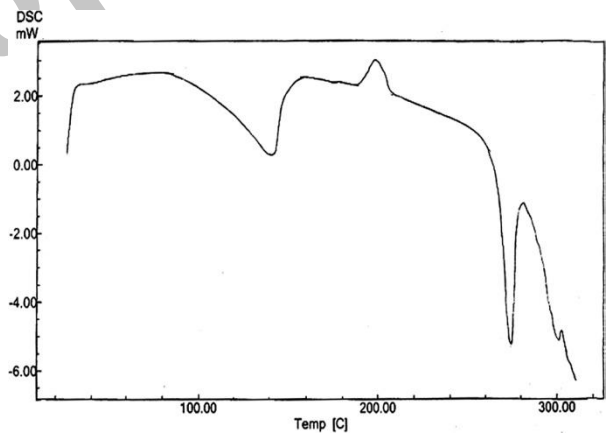

Figure 4. The DSC curve of TER.

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.

References

1. Yamada S, Suzuki M, Kato Y, Kimura R, Mori R, Matsumoto K, et al. Binding characteristics of naftopidil and alpha 1-adrenoceptor antagonists to prostatic alpha-adrenoceptors in benign prostatic hypertrophy. *Life sci* 1992;50(2):127-35.
2. Kazvabe K, Moriyama N, Yamada S, Taniguchi N. Rationale for the use of a-blockers in the treatment of benign prostatic hyperplasia (BPH). *Int J Urol* 1994;1(3): 203-11.
3. Rossi C, Kortmann BB, Sonke GS, Floratos DL, Kiemeney LA, Wijkstra H, et al. Alpha-blockade improves symptoms suggestive of bladder outlet obstruction but fails to relieve it. *J Urol* 2001;165(1):38-41.
4. Anthony CM, Osselton MD, Widdop B. Clark's Analysis of Drugs and Poisons. 3rd ed. London: Pharmaceutical Press;2004.
5. Lamie NT, Badawey AM, Abd El-Aleem AB. Membrane sensors for the selective determination of terazosin hydrochloride dihydrate in presence of its degradation product. *Int J Comprehen Pharm* 2011;2(7):1-5.
6. Atta NF, Darwish SA, Khalil SE, Galal A. Effect of surfactants on the voltammetric response and determination of an antihypertensive drug. *Talanta* 2007;72(4):1438-45.
7. Ghoneim MM, El Ries MA, Hammam E, Beltagi AM. A validated stripping voltammetric procedure for quantification of the anti-hypertensive and benign prostatic hyperplasia drug terazosin in tablets and human serum. *Talanta* 2004;64(3):703-10.
8. Sarsambi PS, Raju SA. Spectrophotometric determination of terazosin hydrochloride. *Asian J Chem* 2001;13(2):760-2.
9. Abdine HH, El-Yazbi FA, Blaih SM, Shaalan RA. Spectrophotometric and spectrofluorimetric methods for the determination of terazosin in dosage forms. *Spectrosc Lett* 1998;31(5):969-80.
10. Prasad CVN, Gautham A, Bharadwaj V, Praimoo P. Quantitative determination of terazosin HCl in tablet preparation by fluorimetry. *Indian J Pharm Sci* 1998;60(3):167-9.
11. Wang CC, Luconi MO, Masi AN, Fernandez L. Determination of terazosin by cloud point extraction-fluorimetric combined methodology. *Talanta* 2007;72(5):1779-85.
12. Srinivas JS, Avadhanulu AB, Anjaneyulu Y. HPLC determination of terazosin hydrochloride in its pharmaceutical dosage forms. *Indian Drugs* 1998;35(5):269-73.
13. Cheah PY, Yuen KH, Liong ML. Improved high-performance liquid chromatographic analysis of terazosin in human plasma. *J Chromatogr B Biomed Sci Appl* 2000;745(2):439-43.
14. Bakshi M, Ojha T, Singh S. Validated specific hplc methods for determination of prazosin, terazosin and doxazosin in the presence of degradation products formed under ich-recommended stress conditions. *J Pharm Biomed Anal* 2004;34(1):19-26.
15. Macedo RO, Nascimento TG, Veras JWE. Compatibility and stability studies of propranolol hydrochloride binary mixtures and tablets for TG and DSC photovisual. *J Therm Anal Calorim* 2002;67(2):483-9.
16. Oliveira GGG, Ferraz HG, Matos JSR. Thermoanalytical study of glibenclamide and excipients. *J Therm Anal Calorim* 2005;79(2):267-70.
17. El-Ries MA, Ahmed IS, Salem WM. The thermal analysis study of the tenoxicam. *J Drug Res* 2010;31(1):89-92.
18. Freitas MN, Alves R, Matos JR, Marchetti JM. Thermal analysis applied in the osmotic tablets pre-formulation studies. *J Therm Anal Calorim* 2007;87:905-11.
19. Yoshida MI, Gomes EC, Soares CD, Cunha AF, Oliveira MA. Thermal analysis applied to verapamil hydrochloride characterization in pharmaceutical formulations. *Molecules* 2010;15(4):2439-52.
20. Attia AK, Hassan NY, El-bayoumi A, Abdel-hamid SG. Thermoanalytical study of alfuzosin HCl. *Int J Curr Pharm Res* 2012;4(3):101-5.
21. Attia AK, Abdel-Moety MM, Abdel-hamid SG. Thermal analysis study of antihypertensive drug doxazosin mesilate. *Arab J Chem* 2012; in press.
22. Giron D. Applications of thermal analysis in the pharmaceutical industry. *J Pharm Biomed Anal* 1986;4:755-70.
23. Horowitz HH, Metzger G. A new analysis of thermogravimetric traces. *Anal Chem* 1963;35:1464-8.
24. Coats AW, Redfern JP. Kinetic parameters from thermogravimetric data. *Nature* 1964;201:68-9.

25. Mathkar S, Kumar S, Bystol A, Olawoore K, Min D, Markovich R, et al. The use of differential scanning calorimetry for the purity verification of pharmaceutical reference standards. *J Pharm Biomed Anal* 2009;49:627-31.
26. Hatakeyama T, Liu Z. Hand Book of Thermal Analysis. London: John Wiley and sons Ltd;1998.
27. British Pharmacopoeia. London: Her Majesty's stationary office; 2011.