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Thermal Analysis Study of Antihypertensive Drugs Telmisartan and Cilazapril

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ABSTRACT

Purpose: The aim of the present work is to study the thermal analysis of telmisartan and cilazapril.
Methods: Thermogravimetry (TGA), derivative thermogravimetry (DTG) and differential thermal analysis (DTA) were used through the work to achieve the thermal analysis study of some antihypertensive drugs, telmisartan and cilazapril.
Results: The results led to thermal stability data and also to the interpretation concerning the thermal decomposition. Thermogravimetry data allowed determination of the kinetic parameters such as, activation energy and frequency factor.
Conclusion: The simplicity, speed and low operational costs of thermal analysis justify its application in the quality control of pharmaceutical compounds for medications.

Introduction

Thermal analysis technique that delivers extremely sensitive measurements of heat change can be applied on a broad scale with pharmaceutical development. These methods provide unique information relating to thermodynamic data of the system studied. The increasing use of the combined techniques is providing more specific information, and thus facilities more rapid interpretation of the experimental curves obtained.[1,2] The need to measure a range of physical parameters has led to the development of numerous techniques such as thermogravimety (TGA), derivative thermogravimetry (DTG) and differential thermal analysis (DTA). In pharmaceutical sciences thermal methods of analysis have found important applications.[3-10] TGA, in which the change in mass of a sample heated at constant rate is recorded and plotted vs. temperature, is an effective method for studying thermal stability and determination the kinetic parameters of the decomposition of drugs. TGA 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. DTA is used for the identification of pharmaceutical and organic compounds.[11-17]

Telmisartan (TMT), 4-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl) methyl]-biphenyl-2-carboxylic acid (Figure 1), is an angiotensin II type I receptor blocker. It is widely used in treatment of hypertension.[18,19] It inhibits the angiotensin II receptor in a way that the effect of angiotensin II is blocked resulting in a decrease of blood pressure.[20]

Cilazapril (CPL), (1S,9S)-9-[[1(S)-1-(Ethoxycarbonyl)-3-phenylpropyl] amino] octahydro-10-oxo-6H-pyridazino[1.2-a][1,2]diazepine-1- carboxylic acid (Figure 1), is a potent and specific angiotensin converting enzyme (ACE) inhibitor which lowers peripheral vascular resistance without affecting heart rate. It is used in the treatment of hypertension and congestive heart failure.[21,22] It also prevents the reabsorption of sodium and water from renal tubules and decreases the heart flow rate.[23,24]

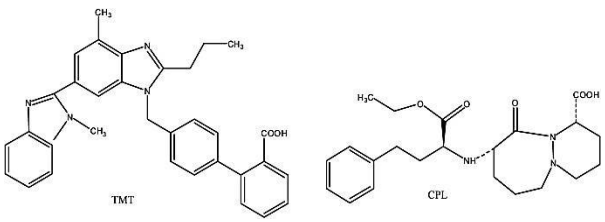

Figure 1. The Structures of TMT and CPL

In the present work two cardiovascular compounds were investigated, Telmisartan and Cilazapril, which

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belong to different groups of antihypertensive drugs, were chosen for study.

Materials and Methods

Telmistran and Cilazapril were obtained from reference standard department (NODCAR)., Egypt. The used drugs have high purity (more than 99%).

Methods

The TGA, DTG and DTA Analysis were made using simultaneous TG-DTA apparatus thermal analyzer (Shimadzu DTG-60H).The experiments were performed between ambient and 1000 °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. The sample mass was kept in the range of 5 mg. α-Al_2O_3 was used as the reference material.

The thermodynamic parameters of decomposition processes of the used drugs namely activation energy (E^*), enthalpy (ΔH^*), entropy (ΔS^*) and Gibbs free energy change of the decomposition (ΔG^*) were evaluated graphically by employing the Horowitz-Metzger and Coats-Redfern relations.

Horowitz-Metzger method[25]

For the first order kinetic process, the Horowitz-Metzger equation can be represented as follow:

$$\log .[\log \frac{W_f}{W_f - W}] = \frac{\theta . E^*}{2.303 RT_s^2} - \log 2.303 \quad (1)$$

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 $\theta = T - T_s$. 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[26]

For the first order kinetic process, the activation energy (E^*) in $J.mol^{-1}$ could be calculated from the following equation:

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

Where ϕ was the heating rate. Since 1-2RT / $E^* \cong 1$, the plot of the left-hand side of equation (2) 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:

$$\Delta S^* = 2.303 [\log (Ah / kT)] R \quad (3)$$

$$\Delta H^* = E^* - RT \quad (4)$$

$$\Delta G^* = H^* - T_s \Delta S^* \quad (5)$$

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

Results and Discussion

Figures (2, 3) show the TGA, DTG and DTA curves of the TMT and CPL, respectively. Table 1 presents the data concerning the main thermal reactions of the examined compounds. Table 2 gives the corresponding DTA reactions.

Thermal analysis of Telmisartan

The TGA and DTG curves of TMT (Figure 2a) show that the compound is thermally stable up to 262 °C. Between 262 and 712 °C, the TGA curve shows mass losses in two steps, while the DTG curve shows one sharp peak and other broad peak. The first step between 262 and 493 °C, a fast process with a mass loss 54.17% is probably due to the thermal decomposition of the compound with the elimination of biphenyl carboxlic acid ($C_{13}H_9O_2$) and $C_5H_9N_2$ groups. The second step between 493 and 712 °C where the mass loss is 45.83% is ascribed to pyrolysis of the compound and the loss of $C_{15}H_{12}N_2$ molecule (Table 1).

The DTA curve of TMT (Figure 2b) shows an endothermic flattened peak with its maximum at 456.63 °C. The main thermal decomposition reaction is endothermic peaks followed by exothermic peaks at 569.27 °C and 610.90 °C may be due to the pyrolysis of the compound. In addition the mentioned peaks, the compound has an endothermic reaction which is not accompanied by weight loss, the reaction has its maximum at 265.84 °C. This reaction is endothermic and may be attributed to melting of the compound. Thermal degradation pattern of TMT was presented in Figure 4a

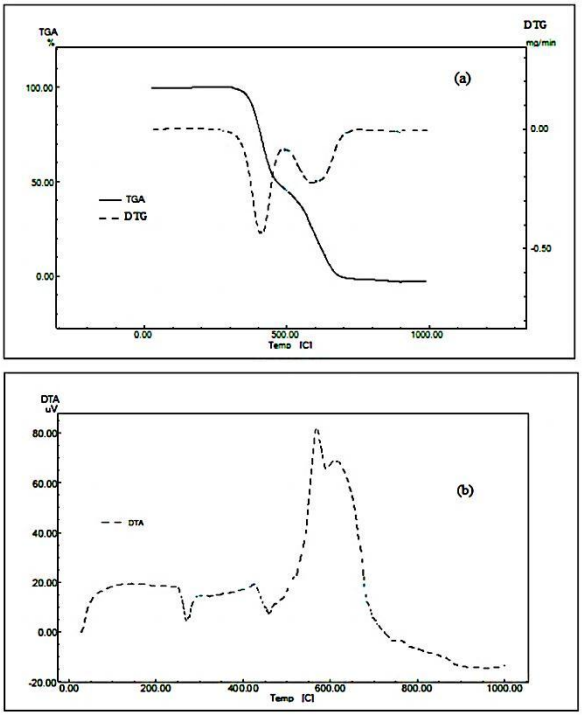

Figure 2. Thermal analysis curves (TGA, DTG and DTA) of TMT

Thermal analysis of Cilazapril

The TGA and DTG curves in (Figure 3a) show that CPL is thermally stable up to 140 °C then the thermal decomposition of CPL occurs. These curves also show that the mass loss up to 663 °C begins with a fast process, followed by slow process. The first step, which involves amass loss of 87.50%, is probably due to the elimination of ethoxycarbonyl, carboxylic, carbonyl, phenylpropyl amino and pyridazino groups. The final loss of 12.50% is ascribed to the pyrolysis of the compound and the loss of C_4H_7 group (Table 1).

The DTA curve of cilazapril (Figure 3b) has a shoulder at the beginning of the first endothermic reaction at 99.65 °C this may be attributed to the partial melting and recrystallization of the compound at 63.21 °C. The endothermic peak at 99.65 °C is due to the melting of the compound. An endothermic peak at 411.19 °C may be due to the decomposition of the compound followed by an exothermic peak at 564.33 °C may be attributed to the pyrolysis of the compound. Thermal degradation pattern of CPL was presented in Figure 4b.

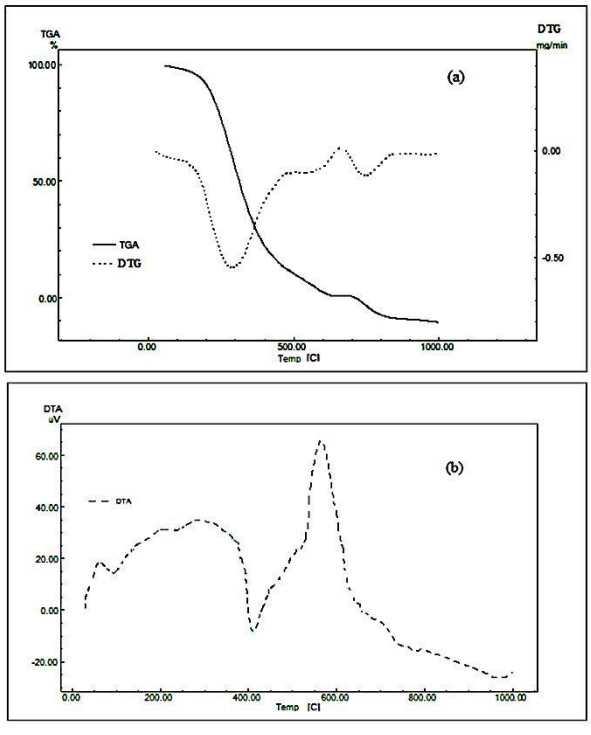

Figure 3. Thermal analysis curves (TGA, DTG and DTA) of CPL

Regarding the thermal stability of the compound, it can be concluded from their decomposition reaction that CPL starts to decompose at lower temperature than TMT. That is, TMT is more thermally stable than CPL.

The melting temperatures of the examined compounds are determined by using the melting points of the compounds obtained by using DTA, and the melting point apparatus, the results are compared with the data stated in the literature.[18,21]

It is clear that results obtained from the DTA figures are comparable with the literature, and hence can be used for the determination the melting point of these TMT and CPL (Table 2).

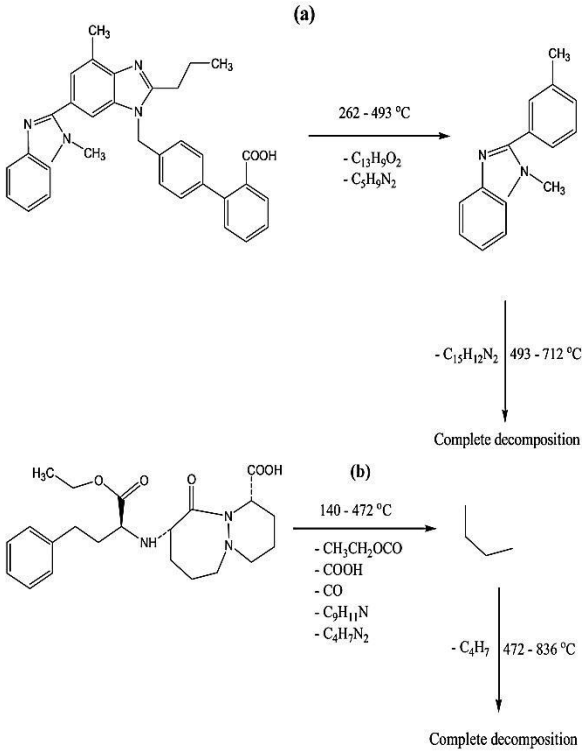

Figure 4. Thermal degradation patterns of TMT (a) and CPL (b)

Table 1. The thermal decomposition reaction of TMT and CPL

Drug	First step			Second step		
	Wt.Loss (%)	Start (°C)	End (°C)	Wt.Loss (%)	Start (°C)	End (°C)
TMT	45.83	262	493	54.17	493	712
CPL	12.50	140	472	87.50	472	836

Table 2. DTA peaks and melting points of TMT and CPL

Drug	Endothermic Peaks (°C)	Exothermic Peaks (°C)	DTA Method(°C)	MeltingPoint Apparatus (°C)
TMT	265.84,456.63	569.27,610.90	265.84	263
CPL	99.65,411.19	564.33	99.65	98

Kinetics and thermodynamic parameters

There were many methods used for the determination of the kinetic parameters. From these, Horowitz and Metzger and Coats and Redfern were applied (Figure 5).

Table 3 shows that the activation energy values (E^*) of TMT are higher than that of CPL. This conclusion is in accordance with previous conclusion for the thermal decomposition reaction of the compounds. The first reaction of CPL needs lower activation energy and hence the compound is the less stable and starts to decompose first.

Table 3. Thermodynamic parameters of the thermal decomposition of TMT and CPL

Drug	Temperature range (°C)	Thermodynamic parameters				
		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)
TMT	262-493	86.50 (99.27)	1.06 $X10^5$ (1.71$X10^6$)	-110.49 (-128.23)	90.60 (95.87)	132.14 (148.17)
CPL	140-472	50.82 (63.65)	4.88$X10^2$ (6.97$X10^3$)	-154.1 (-171.08)	52.63 (61.26)	92.53 (110.50)

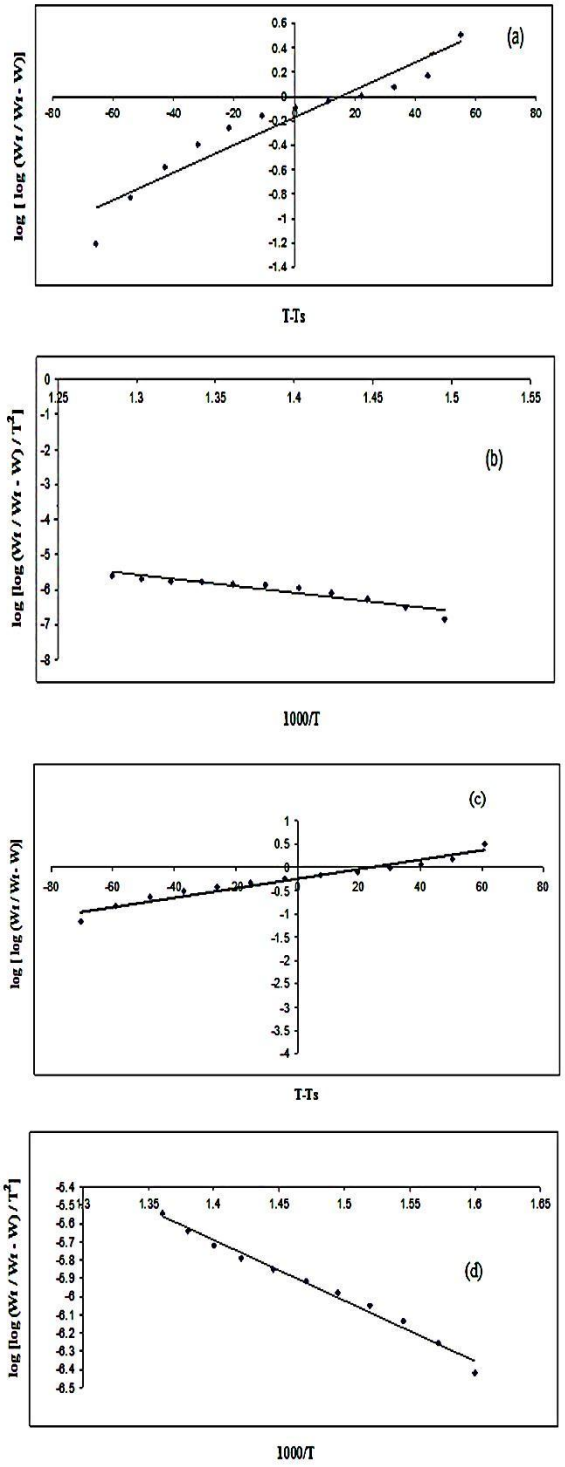

Figure 5. Horowitz-Metzger and Coats-Redfern plots of the decomposition of TMT (a, b) and CPL (c, d), respectively.

Conclusion

The studied compounds TMT and CPL are characterized by having main decomposition reaction and consist of two stages. Besides stability studies, thermal analysis is of value for determining melting temperatures, and water content. The use of clean techniques, and the speed and the simplicity 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 medication.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Fifield FW, Kealey D. Principles and practice of analytical chemistry. 4th ed. London: Blackie Academic & Professional; 1995.
2. Ford JL, Timmings P. Pharmaceutical thermal analysis techniques and applications. Chichister UK: Ellis Harwood; 1989.
3. Giron D. Applications of thermal analysis and coupled techniques in pharmaceutical industry. *J Therm Anal Calorim* 2002;68:335-57.
4. Bruno FP, Caira MR, Monti GA, Kassuha DE, Sperandeo NR. Spectroscopic, thermal and X-ray structural study of the antiparasitic and antiviral drug nitazoxanide. *J Mol Struct* 2010;984(1-3):51-7.
5. Zayed MA, Fahmey MA, Hawash MF. Investigation of diazepam drug using thermal analyses, mass spectrometry and semi-empirical MO calculation. *Spectrochim Acta A Mol Biomol Spectrosc* 2005;61(5):799-805.
6. Wassel AA, El-Ries MA, Hawash MF. Structural investigation of captopril drug, using thermal analysis, mass spectral fragmentation and semi-empirical MO-calculations. *J Pharm Res* 2010;3(3):618-23.
7. Radha S, Gutch PK, Ganesan K, Vijayaraghavan R, Suman J, Subodh D. Thermal analysis of interactions between an oxime and excipients in

some binary mixtures by differential scanning calorimetry and thermagravimetric analysis. *J Pharm Res* 2010;3(3):590-5.
8. Oliveira GGG, Ferraz HG, Matos JSR. Thermoanalytical study of glibenclamide and excipients. *J Therm Anal Calorim* 2005;79(2):267-70.
9. Attia AK, Ibrahim MM, El-Ries MA. Thermal analysis of some antidiabetic pharmaceutical compounds. *Adv Pharm Bull* 2013;3(2):419-24.
10. Attia AK, Mohamed Abdel-Moety M. Thermoanalytical investigation of terazosin hydrochloride. *Adv Pharm Bull* 2013;3(1):147-52.
11. Tita B, Fulias A, Stefanescu M, Marian E, Tita D. Kinetic study of decomposition of ibuprofen under isothermal conditions. *Rev Chim-Bucharest* 2011;62(2):216-21.
12. Tomassetti M, Catalani A, Rossi V, Vecchio S. Thermal analysis study of the interactions between acetaminophen and excipients in solid dosage forms and in some binary mixtures. *J Pharm Biomed Anal* 2005;37(5):949-55.
13. El-Ries MA, Abo-Attia FM, El-Bayoumi A, Eman GS. Thermal characterization of leflunomide. *Insight Pharm Sci* 2011;1(2):18-23.
14. 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.
15. Abdel-Razeq SA, Salama NN, Abdel-Atty Sh, El-Kosy N. Thermoanalytical study and purity determination of azelastine Hydrochloride and emedastine difumarate. *Pharm Anal Acta* 2012;3(8):2153-435.
16. Haung Y, Ycheng K, Dalimore AD. The thermal analysis study of the drug captopril. *Thermochim Acta* 2001;367:43-58.
17. Elries MA, Ahmed IS, Salem WM. The Thermal analysis study of the tenoxicam. *J Drug Res Egypt* 2010;31(1):89-92.
18. Neil MJO. The Merck index, an encyclopedia of chemicals, drugs and biologicals, 14th ed. New Jersey: Merck research laboratories, Whitehouse station; 2006.
19. Wexler RR, Greenlee WJ, Irvin JD, Goldberg MR, Prendergast K, Smith RD, et al. Nonpeptide angiotensin II receptor antagonists: the next generation in antihypertensive therapy. *J Med Chem* 1996;39(3):625-56.
20. Willenheimer R, Dahlof B, Rydberg E, Erhardt L. AT1-receptor blockers in hypertension and heart failure: clinical experience and future directions. *Eur Heart J* 1999;20(14):997-1008.
21. Szucs T. Cilazapril. *Drugs* 1991;41 Suppl 1: 18-24.
22. Natoff IL, Nixon JS, Francis RJ, Klevans LR, Brewster M, Budd J, et al. Biological properties of the angiotensin-converting enzyme inhibitor cilazapril. *J Cardiovasc Pharmacol* 1985;7(3):569-80.
23. Foye OW. Principles of medicinal chemistry. 3rd ed. Philadelphia: Lea & Jebliger;1989.
24. Gilman GA, Rall TW, Nies AS, Taylor P. The pharmacological basis of therapeutics. 8th ed. New York: Pergamon press; 1990.
25. Horowitz HH, Metzger G. A new analysis of thermogravimetric traces. *Anal Chem* 1963;35(10):1464-8.
26. Coats AW, Redfern JP. Kinetic parameters from thermogravimetric data. *Nature* 1964;201(4914):68-9.