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Original Article

INVESTIGATION ON THERMAL STABILITY AND PURITY DETERMINATION OF TWO ANTIHYPERTENSIVE DRUGS, VALSARTAN AND LOSARTAN POTASSIUM

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ABSTRACT

Objective: The thermal behavior of two antihypertensive drugs: Valsartan (VAL) and Losartan potassium (LOS) was investigated using different thermal techniques. These include thermogravimetry (TGA), derivative thermogravimetry (DTG) and differential scanning calorimetry (DSC).

Methods: Thermogravimetric data obtained from first step of decomposition of valsartan and losartan allowed the determination of kinetic parameters such as activation energy (Ea), frequency factor (A), order of reaction (n) and enthalpy of decomposition (ΔH). The purity of valsartan and losartan were determined by differential scanning calorimetry.

Results: The thermal degradation of losartan and valsartan was followed a first-order kinetic behavior and evaluation of the relative thermal stabilities showed that LOS is more thermally stable than VAL. The decomposition modes were investigated and the fragmentation pathway of losartan was taken as example, to correlate the thermal decomposition with mass spectrometry. The purity of valsartan and losartan determined by differential scanning calorimetry was found to be 99.84 % and 99. 91 %, respectively, which was in good agreement with the pharmacopoeial results.

Conclusion: Thermal analysis justifies its application in quality control of pharmaceutical compounds due to its simplicity, sensitivity and low operational costs.

INTRODUCTION

Valsartan and losartan potassium are non-peptide, orally active angiotensin II (Type AT_1) receptor antagonists employed in the management of essential hypertension [1]. Valsartan is designated as *N*-(1-oxopentyl)-*N*-{[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl}-*L*-valine (Fig.1a). Losartan potassium, a potassium salt of: (2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl) biphenyl-4-yl] methyl}-1*H*-imidazol-5-yl) methanol (Fig.1b). Different analytical methods have been reported for the analysis of valsartan. They include chromatographic [2-8], electrochemical [9, 10] and spectrophotometric [11-13] methods. Many chromatographic methods were described for the analysis of losartan [2, 14-21]; spectrophotometric [22-24] and electrophoretic [25] methods were also reported.

Thermal analysis is a group of techniques in which a physical property of a substance and/or its reaction products is measured as a function of temperature whilst the substances subjected to a controlled temperature program. They include techniques such as thermogravimetry (TGA), derivative thermogravimetry (DTG) and differential scanning calorimetry (DSC). In a thermogravimetric analysis the mass of a sample in a controlled atmosphere is recorded as a function of temperature or time as the temperature of the sample is increased [26]. TGA/DTG are commonly employed in research and testing to determine degradation temperatures, absorbed moisture content of materials, decomposition and kinetic parameters[27]. Differential scanning calorimetry (DSC) is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. DSC is 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 [28]. It can be successfully used as a complementary and or an alternative technique to verify the purity of a compound during the certification or the re-certification, provided that the material is at least 98% and does not melt with decomposition.

As indicated in the United States and British Pharmacopoeias in general chapters on thermal analysis [2,29], the purity of primary reference standards assigned using chromatographic or spectroscopic methods must be independently verified by methods such as DSC where appropriate.

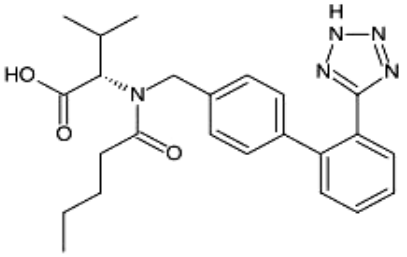


Fig. 1a: Chemical structure of valsartan

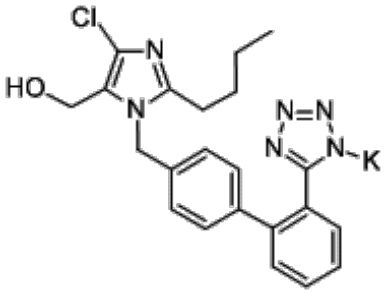


Fig. 1b: Chemical structure of losartan potassium

A thorough literature survey revealed few thermal studies for valsartan (especially phase identification) [30] and compatibility with excipients [31]. No reported data were published for application of TGA/DTG for investigation of thermal stability and kinetic parameters of the two drugs and no references have been found for their purity determination using differential scanning calorimetry. Therefore, the objective of this work was to characterize and compare the thermal stabilities and kinetic parameters of valsartan and losartan potassium using TGA/DTG data and evaluating their degree of purity using DSC technique in comparison with Pharmacopeial methods.

MATERIALS AND METHODS

Materials

Valsartan was kindly supplied from Novartis Pharmaceuticals (Egypt). Its purity was found to be 99.51 % according to the official method [2]. Losartan potassium was provided by Hikma Company, Cairo-Egypt, its purity was found to be 99.83 % according to the Pharmacopeial method [2].

Instrumentation and methods

Thermogravimetry and derivative Thermogravimetry (TGA/DTG)

TGA/DTG curves of drug substances were recorded using simultaneous Shimadzu thermogravimetric analyzer TGA-60 H with TA 60 software in the dry nitrogen atmosphere at a flow rate of 30 mL/min in Platinum crucible with an empty platinum crucible as a reference. The experiments were performed from ambient temperature up to 900 ℃ with a heating rate of 10 ℃/min. The sample mass was about 4 mg of the drug without any further treatment. The kinetic parameters of decomposition were calculated from TGA/DTG curves by using Coats and Redfern [32] and Horowitz and Metzger [27] relations which applied for the first order kinetic process.

Differential scanning calorimetry (DSC)

The DSC curves of valsartan and losartan were recorded using Shimadzu-DSC 50, in dynamic nitrogen atmosphere with a constant flow rate of 30 ml/min and heating rate of 5 °C/min, up to temperature 300 °C using a mass of about 2 mg of sample packed in platinum pan. DSC equipment was preliminarily calibrated with standard reference of indium.

RESULTS AND DISCUSSION

General aspects and characterization of the investigated Compounds by TGA/DTG

Valsartan: The TGA/DTG curves of valsartan presented in fig. 2a shows three mass loss regions.

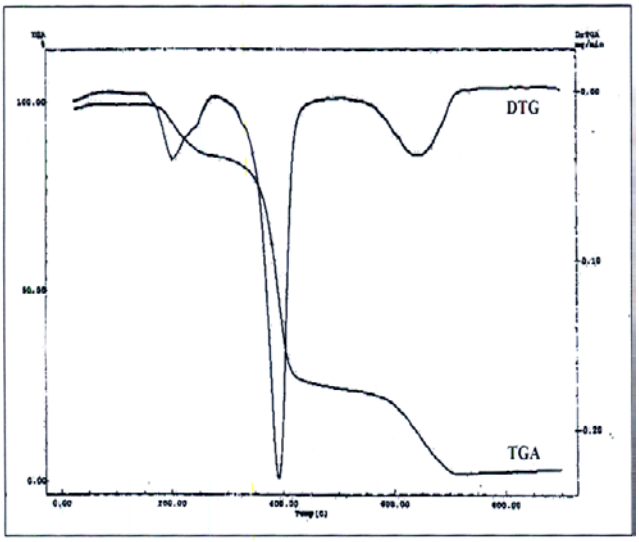


Fig. 2a: TGA-DTG curves of valsartan

The first decomposition step starts early at 155 °C and ends at 295 °C, it shows a mass loss of 18.10 %, which may be attributed to loss of C_5H_8O from the amide side chain (cal 19.30%). Before this step and between 65 °C and 70 °C there was a mass loss of about 1.40 % and is assigned to the dehydration process.

After 295 °C the drug loses about 54.22 % (calc 53.44 %) of its weight in a second and fast step (295-440 °C), may be due to loss of $C_{12}H_{15}N_3O_2$. The third and last step between 440°C and 775°C occurs as a slow process with a loss of 26.20 % (cal 27.06%), it may be due to loss of $C_7H_6N_2$ and final pyrolysis of the drug (table 1).

Table 1: Thermal decomposition data of TGA/DTG curves of valsartan

Temperature Range °C	Observed mass loss %	Calculated mass loss %	Assignment
65-70	1.40%	Not more than 2(*)	-H_2O dehydration process
155-295	18.10	19.30	Loss of C_5H_8O
295-440	54.22	53.44	Loss of $C_{12}H_{15}N_3O_2$
440-775	26.20	27.06	Loss of $C_7H_6N_2$

* United states pharmacopeia [2]

Losartan potassium

Losartan potassium has different thermal behavior, the TGA/DTG curves (fig. 2b) demonstrate that the drug is thermally stable up to 275°C and then it decomposes in three consecutive steps. The first step of decomposition begins at about 275°C and ends at 365 °C, the drug loses about 25.20 % of its weight which may be due to the loss of C_5H_8NCl (calc 25.40 %) %) and a second step begins directly after 365 °C and ends at 535 °C with mass loss 29.20 % (calc 29.50 %) which may be attributed to loss of $C_3H_3KN_3O$. The third and final step was observed between 535°C and 860 °C with a total mass loss of about 45.50 % (calc 44.90 %) and may be due to loss of $C_{14}H_{11}N_2$. As shown by DTG curve this step occurs in two stages: 1^{rst} stage between 535°C and about 750 °C with a mass loss of 19.40 % (cal 19.30 %) which may be attributed to loss of C_7H_5 group and 2nd stage between 750 °C and 860 °C with a mass loss of 26.10 % (calc 25.60 %) and is ascribed to final pyrolysis of the remaining part of the compound. Results are presented in table 2.

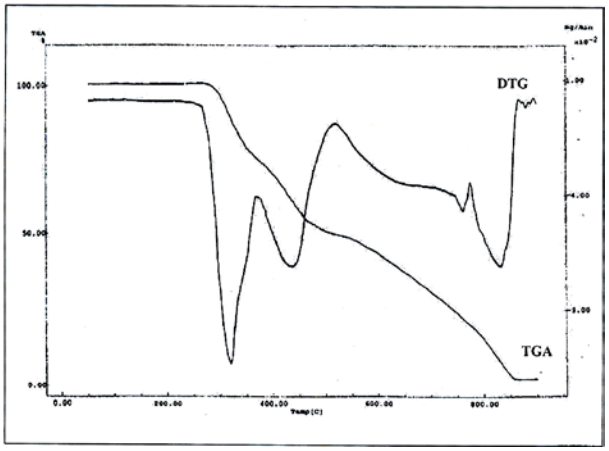
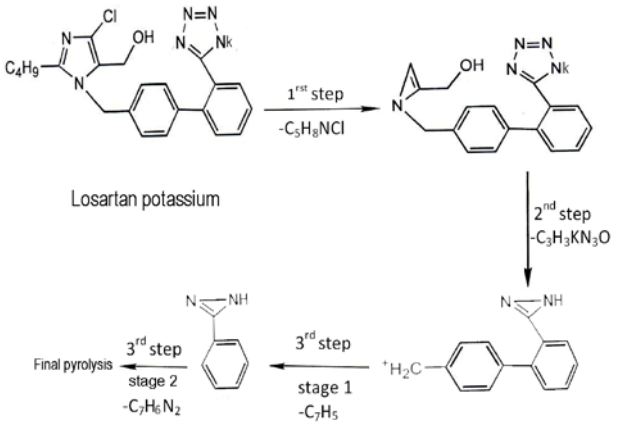


Fig. 2b: TGA-DTG curves of losartan potassium

The proposed fragmentation pattern and tandem mass spectrum of losartan [20] show good correlations between mass fragmentation and suggested thermal degradation pattern of losartan potassium (Scheme 1).



Scheme 1: Suggested thermal degradation pattern of Losartan potassium in correlation with Mass spectral fragmentation pathway [20]

Kinetic analysis

Results obtained by the first step of decomposition suggest that losartan is thermally stable than valsartan. These results were confirmed by calculation of kinetic parameters such as activation energy (Ea) and the frequency factor (A) in addition to enthalpy change (**Δ**H), which was obtained from Coats-Red fern [32] and Horowitz-Metzger [27] methods.

(a) Coats- Redfern method [32]

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

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

ϕ is the heating rate, A is the frequency factor, W_f is the mass loss at the completion of the decomposition reaction, W is the mass loss up to temperature T, R is the gas constant. 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 or frequency factor A (table 3) was obtained from the intercept (fig. 3 a & 3 b).

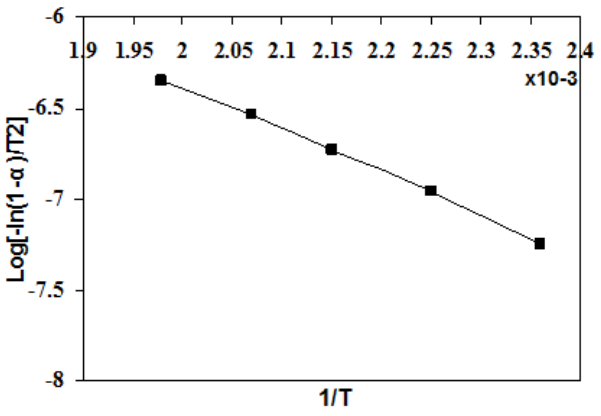


Fig. 3a: Coats-Redfern plot for valsartan α=W/Wf

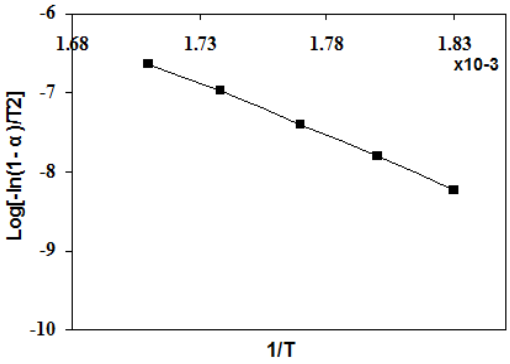


Fig. 3b: Coats-Redfern plot for losartan α=W/Wf

(b) Horowitz-Metzger method (HM) [27]

For the first order kinetic process (n=1), the Horowitz-Metzger equation can be represented as follows:

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

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, Ts was the DTG peak temperature and θ = T-Ts. A plot of log [log W_f/(W_f-W)] against θ (fig. 4 a &4 b) would give a straight line and E* could be calculated from the slope (table 3).

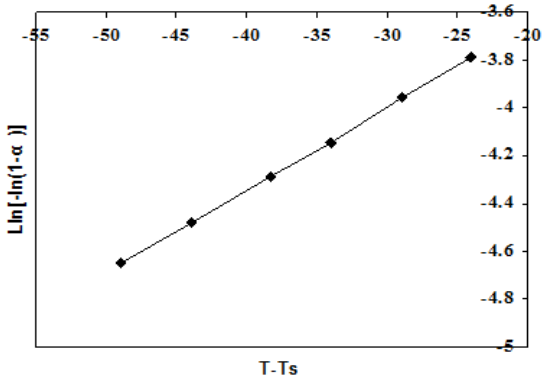


Fig. 4a: Horowitz-Metzger plot for valsartan, α=w/wf

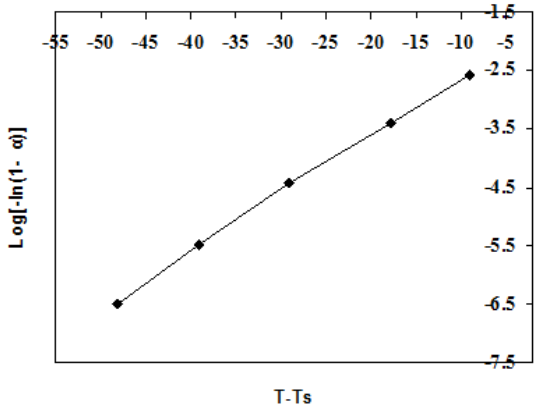


Fig. 4b: Horowitz-metzger plot for losartan, α=w/wf

Enthalpy change ΔH was calculated using the following equation:

ΔH = E-RT

Comparison of the activation energies and other kinetic parameters (obtained from the first stage of thermal decomposition) showed that the losartan is more thermally stable than valsartan (table 3).

Application of differential scanning calorimetry for purity verification of valsartan and losartan potassium

Main advantages of purity analysis by DSC are minimal sample requirement and shorter analysis time as compared to other methods of analysis especially chromatographic analysis. The determination of purity is based on the assumption that impurities lower the melting point of a pure substance whose melting is characterized by a melting point (T_0).

The melting transition of a pure, 100% crystalline substance should be infinitely sharp, but impurities will broaden the melting range and lower the melting point [28].

Table 2: Thermal decomposition data of TGA/DTG curves of Losartan potassium

Temperature Range °C	Observed mass loss %	Calculated mass loss %	Assignment
275-365	25.20	25.40	Loss of C_5H_8NCl
365-535	29.20	29.50	Loss of $C_3H_3KN_3O$
535-860	45.50	44.90	Loss of $C_{14}H_{11}N_2$
Stage (1)	19.40	19.30	Loss of C_7H_5
535-750	26.10	25.60	Loss of $C_7H_6N_2$
Stage (2)			
750-860			

Table 3: Kinetic parameters obtained by the methods of Coats and Redfern (CR) and Horowitz and Metzger (HM) for valsartan and losartan potassium

Dug	Temperature range °C	E (KJ/mol) CR HM	A (sec^{-1}) CR	Reaction Order (n)	ΔH kJ/mol CR HM
Valsartan	145-295	47.31	$2.72x10^2$	1	43.46
		56.03			52.16
losartan	275-365	243.74	1.65x10[17]	1	238.20
		250.32			245.18

The effects of impurities on T_0 of valsartan and losartan were determined by DSC method based on the Van't Hoff equation:

$$T_f = T_0\text{-}[(RT^2_0\, X/\Delta H_f).1/F]$$

Where T_f is the melting temperature of the sample, T_0 is the melting point of pure substance, 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 [28]. By plotting the inverse of the fraction of the sample melted against their corresponding temperature and making the necessary correction for linearization [33], a straight line results from which T_0 and X can be calculated.

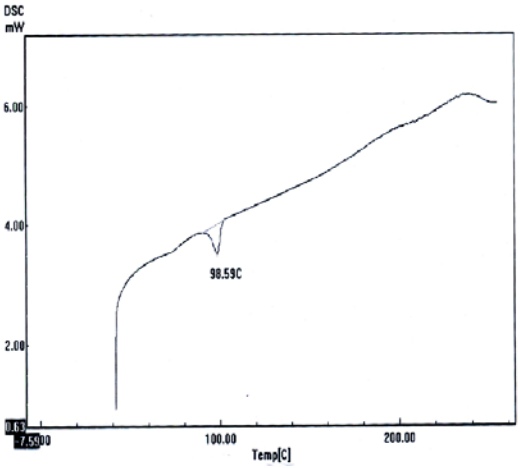


Fig. 5a: DSC profile of valsartan

DSC thermogram of valsartan is shown in fig. 5a, an endothermic peak was observed at 98.59ºC corresponding to melting point of valsartan sample, integration of the melting endotherm yielded an enthalpy of fusion equal 15.31 J/g. No exotherm were observed near right to the melting endotherm since valsartan begins to decompose at about 155 °C as previously shown by TG/DTG curves.

Losartan potassium was subjected to DSC analysis; the thermogram is shown in fig. 5b. A sharp endotherm was observed at 265.51 °C corresponding to sample melting point with an enthalpy of fusion equal to 100.22 J/g. As, shown in the dsc thermogram, an exothermic transition was observed after the endothermic melt indicating start of decomposition of the drug, which was previously confirmed by TG/DTG results.

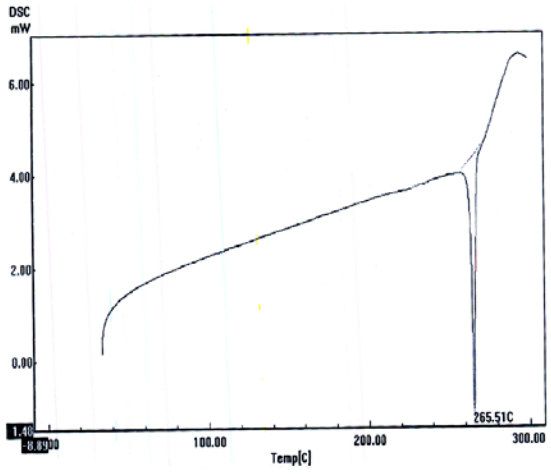


Fig. 5b: DSC profile of losartan potassium

Applying Van't Hoff equation and plotting 1/F against their corresponding temperature T_f (in Kelvin, K), and after making the necessary correction, linear plots were obtained (fig. 6a & 6b), whose zero intercept is the extrapolated melting point, T_0, of theoretically pure substance and melting point depression ΔT were then calculated (table 4). Mole fractions of impurities (X) were determined and the results revealed that the samples valsartan and losartan were very pure samples (99.84% and 99.91 %, respectively). These values were in close agreement with the results obtained by using the official methods [(2)], confirming low impurity content (table 4).

Table 4: Melting point and degree of purity of valsartan and losartan potassium calculated from DSC data and official methods

Drug	Observed mp (K) (°C)	T_0 (K) (°C)	ΔT (K) (°C)	Degree of purity % DSC official [2] methods	
VAL	371.74	371.95	0.21	99. 84	99. 51
	98.59	98.80	0.21		
LOS	538.66	538.80	0.14	99. 91	99. 83
	265.51	265.65			

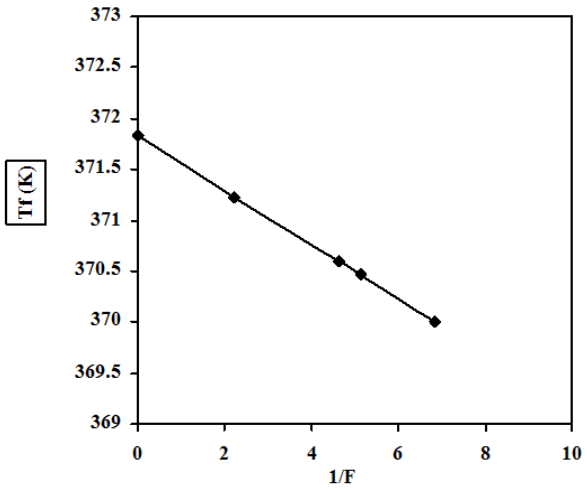


Fig. 6a: Van't Hoff Plot of temperature (T) vs reciprocal of fraction (1/F) for valsartan

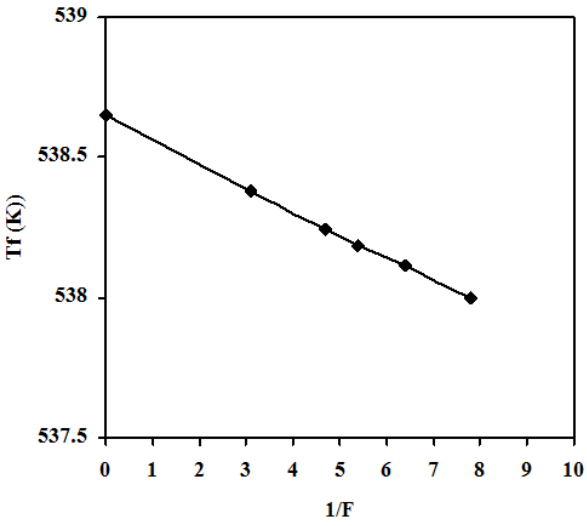


Fig. 6b: Van't Hoff Plot of temperature (T) vs reciprocal of fraction (1/F) for losartan potassium

CONCLUSION

The thermal stabilities of valsartan and losartan potassium using different thermal techniques (TGA/DTG and DSC) were studied. The kinetic studies of the first decomposition step of the two drugs showed a thermal behavior characteristic to first order and indicate that losartan is more thermally stable than valsartan. The correlation between mass spectra and thermal decomposition behavior of losartan revealed the good correlation between the two techniques. DSC method describes the determination of purity of materials greater than 98 mole percent purity but the advantages of purity analysis by DSC are minimal sample requirement and shorter analysis time as compared to many techniques especially chromatographic analysis. For losartan and valsartan purity results obtained by DSC are in agreement with the official pharmacopoeia. The simplicity, speed, and low operational costs of DSC analysis of pharmaceuticals justify its application in quality control.

ACKNOWLEDGEMENT

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CONFLICT OF INTERESTS

Declared None

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