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Research Article

Thermal Analysis Investigation of Dapoxetine and Vardenafil Hydrochlorides using Molecular Orbital Calculations

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Abstract

Purpose: Thermal analysis techniques have been used to study the thermal behavior of dapoxetine and vardenafil hydrochlorides and confirmed using semi-empirical molecular orbital calculations.

Methods: Thermogravimetric analysis, derivative thermogravimetry, differential thermal analysis and differential scanning calorimetry were used to determine the thermal behavior and purity of the drugs under investigation. Thermodynamic parameters such as activation energy, enthalpy, entropy and Gibbs free energy were calculated.

Results: Thermal behavior of DAP and VAR were confirmed using by semi-empirical molecular orbital calculations. The purity values were found to be 99.97% and 99.95% for dapoxetine and vardenafil hydrochlorides, respectively. The purity of dapoxetine and vardenafil hydrochlorides is similar to that found by reported methods according to DSC data.

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

Introduction

Dapoxetine hydrochloride (DAP) is designated chemically as N, N dimethyl-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine. It is mainly used as selective short acting potent serotonin reuptake inhibitor (SSRI). It is effective for the treatment of premature ejaculation in men.[1,2]

Vardenafil hydrochloride (VAR), is chemically 2-[2-ethoxy-5(4-ethyl-piperazine-1-sul-phonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo 5,1-f] [1-3] triazin-4-one hydrochloride. It is used to treat erectile dysfunction.[3]

Thermal analysis has been an extremely important analytical tool within the pharmaceutical industry where the rapid advances in pharmaceutical industries have led to an increased demand for the chemical and structural information about the pharmaceutical systems. Thermal analysis is a group of techniques in which the variation of a physical property of a substance is measured as a function of temperature. The most commonly used are those which measure changes of mass or changes in energy of a sample of a substance. These techniques such as thermogravimetric analysis (TGA), derivative thermogravimetry (DrTGA), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) provide unique information in relation to thermodynamic data of the system studies. Several studies have been reports the importance of thermal analysis in characterization, polymorphism identification, and purity evaluation of drugs, compatibility studies for the pharmaceutical formulation, stability and drugs thermal decomposition.[4-16]

No previous publications were made before for the study of thermal behavior of DAP and VAR. Therefore, the present work aimed to study the thermal behavior of DAP and VAR using different techniques such as TGA, DrTGA, DTA and DSC, the results were confirmed using semi-empirical molecular orbital calculations to determine the weakest bonds ruptured during thermal degradation of the used drugs. Therefore, the correct pathway of degradation knowing this structural session of bonds can be used to predict the active sites of theses drugs responsible for its chemical reactivities.[17-21]

Materials and Methods

Materials

Dapoxetine hydrochloride, (Batch number: 511DAPF017, purity 99.92%.) and Joypox tablets (60 mg DAP *per* tablet) were provided from Eva Pharma, Egypt and South Egypt for Drug Industries Company (SEDICO) for Inspire Pharmaceutical Company (IPC Pharma), Egypt, respectively.

Vardenafil hydrochloride trihydrate, (Batch number: UT 2130107, purity 99.94%) and Rectivard tablets (20 mg VAR *per* tablet) were provided from Eva Pharma, Egypt and Marcyrl Pharmaceutical Industries Company, El-Obour City, Egypt, respectively.

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Instruments and 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 ^{o}C. The temperature program had a heating rate 10 °C min^{-1}. Dry nitrogen at a flow rate of 30 mL min^{-1} was used as the purge gas. α-Al_2O_3 was used as the reference material.

Semi-empirical molecular orbital (MO) calculations were done by using hyperchem 8.0 program (AM1 method), the most important parameters calculated using MO calculation are bond length, bond order and charge distribution.[17-21]

Thermodynamic parameters such as Arrhenius constant (A), activation energy (E), enthalpy (ΔH), entropy (ΔS) and Gibbs free energy (ΔG) were calculated using Horowitz-Metzger and Coats-Redfern methods.[22,23]

DSC curves were measured on Shimadzu DSC-50 cell. Approximately 3 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 in temperature range from 25 to 500 °C in nitrogen atmosphere with flow rate of 30 mL min^{-1} using heating rate of 10 °C min^{-1}. DSC equipment was preliminary calibrated with standard of indium.

Results and Discussion

Thermal analysis of DAP and VAR

Figure 1 shows the TGA, DrTGA and DTA curves of DAP and VAR. DAP is thermally stable up to 158.12 °C, and then decomposes in two steps. The thermal decomposition of VAR occurs in five consecutive steps.

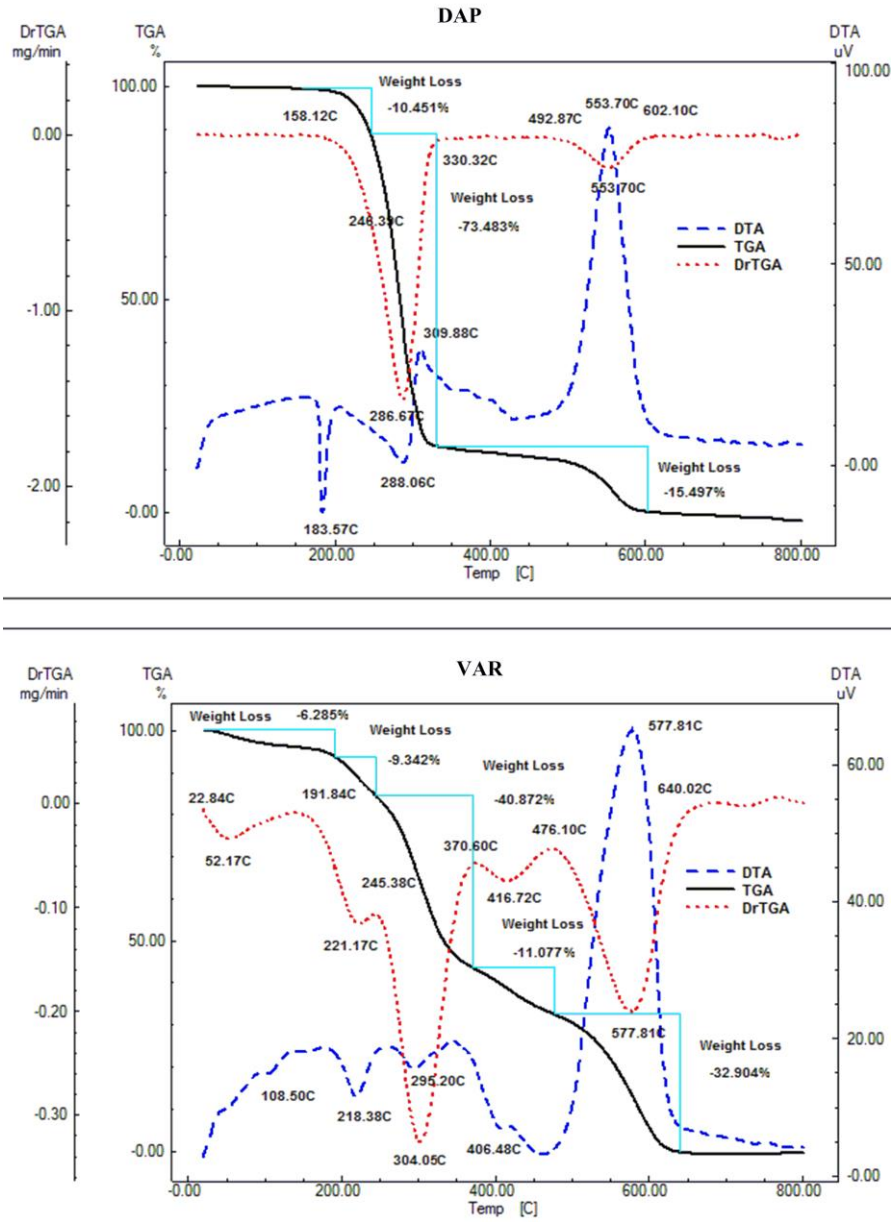

Figure 1. TGA, DrTGA and DTA curves of DAP and VAR.

For DAP, the first step occurs in two consecutive stages, the first stage at temperature range 158.12-246.39 °C is due to the loss of HCl molecule (Mass loss: Found 10.451%, Calc. 10.676%) and the second stage is due to the loss of $C_{17}H_{19}NO$ (Mass loss: Found 73.483%, Calc. 74.0%) at 246.39-330.32 °C. The second step occurs at 330.32-602.10 ^{o}C with the loss of C_4H_4 (Mass loss: Found 15.497%, Calc. 15.21%). These results indicate the compatibility between mass fragmentation and thermal degradation of DAP.[24]

The DTA curve of DAP shows two endothermic peaks and two exothermic peaks. The first endothermic peak at 183.57 °C is sharp and may be attributed to the melting point of DAP, this value is close to the reported melting point of DAP (179-183 °C).[25] The second endothermic peak at 288.06 °C and the exothermic peak at 309.88 °C are broad and may be due to the loss of HCl and $C_{17}H_{19}NO$. Very strong and sharp exothermic peak at 553.70 °C may be due to the loss of C_4H_4.

For VAR, the first step occurs in the temperature range from 22.84 °C to 191.84 °C with the loss of HCl molecule 6.285% (Mass loss: Found 6.285%, Calc. 6.303%). The second step occurs at 191.84-245.38 °C with the loss of three molecules of water (Mass loss: Found 9.342%, Calc. 9.324%). The third step occurs at 245.38-370.60 °C due to the mass losses of SO_2, $C_6H_{13}N_2$, C_3H_7 and CH_3 (Mass loss: Found 40.872%, Calc. 40.580%). The fourth step occurs at 370.60-476.10 °C due to loss of C_3N_2 (Mass loss: Found 11.077%, Calc. 11.051%). It is followed by the fifth practical weight loss of 32.904%. This loss may be due to the complete decomposition of $C_{10}H_7N_2O_2$ that occurs at 476.10-640.02 °C (Mass loss: Calc. 32.291%). These results indicate that, the compatibility between mass fragmentation and thermal degradation of VAR.[26]

The DTA curve of VAR shows four endothermic peaks and an exothermic peak. The first weak endothermic peak at 108.50 °C may be attributed to the loss of HCl molecule. The second endothermic peak at 218.38 °C may be attributed to melting point of VAR, this value is very close to the reported melting point of VAR (218 °C)[25] the melting process is accompanied with the loss of three molecules of water. The third endothermic peak at 295.20 °C may be due to the losses of SO_2, $C_6H_{13}N_2$, C_3H_7 and CH_3. The fourth endothermic peak at 406.48 °C may be due to the loss of C_3N_2. Very strong and sharp exothermic peak at 577.8 °C may be due to the loss of $C_{10}H_7N_2O_2$. Figure 2 shows the thermal decomposition pattern of DAP and VAR.

MO calculations of DAP and VAR

MO calculations depending on numbering system of DAP and VAR give variable information about the structure of the molecules which actually be used to support the experimental results. Figure 2 shows the numbering of DAP and VAR.

MO calculation data for DAP reveal that the loss of $C_{17}H_{19}NO$ in the first step of decomposition is due to the rupture of C13-C14 bond (bond length = 1.536 Å and bond order = 0.975), C12-C13 bond (bond length = 1.528 Å and bond order = 0.982), C14-C15 bond (bond length = 1.512 Å and bond order = 0.967), C14-N21 bond (bond length = 1.507 Å and bond order = 0.964), N21-C22 bond (bond length = 1.483 Å and bond order = 0.994), N21-C23 bond (bond length = 1.480 Å and bond order = 0.992) and O11-C12 bond (bond length = 1.431 Å and bond order = 0.950). The loss of C_4H_4 in the second step is due to the rupture of C3-C4 bond (bond length = 1.422 Å and bond order = 1.218) and C5-C6 bond (bond length = 1.421 Å and bond order = 1.221).

MO calculations of VAR revealed that in the third decomposition step, the losses of SO_2 and $C_6H_{13}N_2$ are due to the rupture of C1-S24 bond (bond length = 1.786 and Å bond order = 0.712), S24-N27 bond (bond length = 1.772 Å and bond order = 0.695), the losses of C_3H_7 and CH_3 are due to the rupture of C17-C21 bond (bond length = 1.488 Å and bond order = 0.971), C19-C20 bond (bond length = 1.473 Å and bond order = 0.998), respectively. The rupture of C13-C14 bond (bond length = 1.449 Å and bond order = 1.001) and N11-N12 bond (bond length = 1.388 Å and bond order = 1.021) causes the loss of C_3N_2 and $C_{10}H_7N_2O_2$ for the fourth and the fifth steps, respectively.

Thermodynamic parameters of DAP and VAR

Horowitz-Metzger (HM) and Coats-Redfern (CR) methods were applied for calculating the activation energy (E) values required for the mass losses during thermal decomposition steps of DAP and VAR and the other thermodynamic parameters (A, ΔS, ΔH and ΔG). The negative values of ΔS may refer to the stability of the loosed fragments obtained as a result of thermal decomposition of DAP and VAR, on the other hand the of the second step of decomposition of DAP shows high positive values of ΔS (168.45 (HM) and 123.17 (CR) J mol^{-1} K^{-1}) may refer to the high activity and volatility of the loosed C_4H_4 fragments. The results are listed in Table 1, from these results we conclude that DAP is more stable than VAR.

Determination of purity of DAP and VAR

The determination of purity of the used compounds in chemistry is very important, chromatographic methods are used to determine purity of the used compounds in comparison with a standard samples. On the other hand, DSC technique can be used for the determination of purity based on the assumption that the impurities will lower the melting point of a pure substance. The melting transition of 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.[27] 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 fraction of sample melted at T_f, and x is mole fraction of impurities in the original sample.

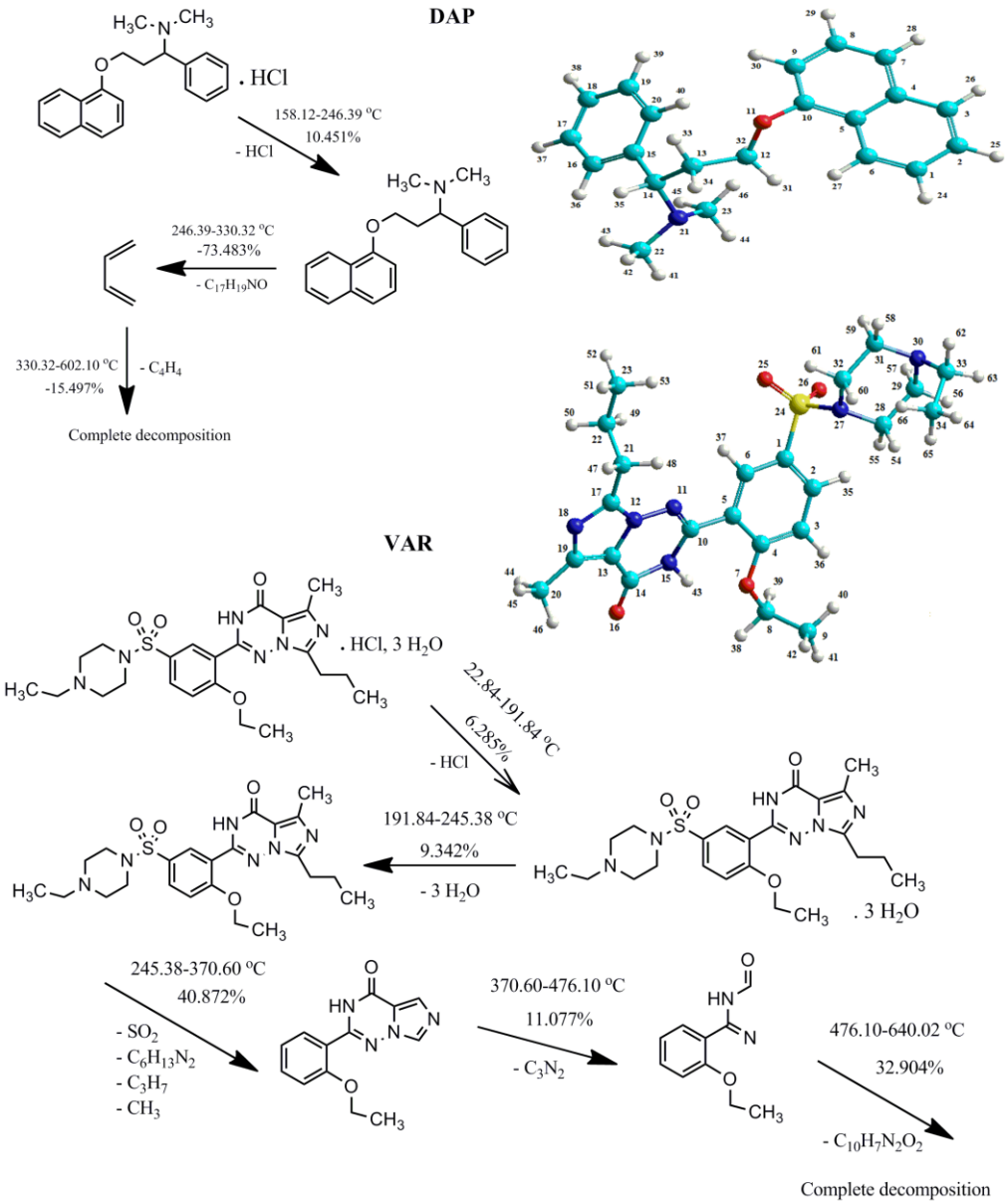

Figure 2. Thermal decomposition of patterns, numbering of DAP and VAR.

Table 1. Thermodynamic parameters of thermal decomposition of DAP and VAR.

	Temperature range (°C)	E (KJ mol^{-1}) HM (CR)	A (S^{-1}) HM (CR)	ΔS (J mol^{-1} K^{-1}) HM (CR)	ΔH (KJ mol^{-1}) HM (CR)	ΔG (KJ mol^{-1}) HM (CR)
DAP	158.12-330.32	137.94 (122.17)	3.97 x 10^{12} (4.99 x 10^{10})	-8.96 (-45.36)	133.29 (117.51)	138.30 (142.90)
	492.87-602.10	352.00 (334.82)	1.08 x 10^{22} (4.67 x 10^{19})	168.45 (123.17)	345.13 (327.94)	205.87 (226.11)
VAR	22.84-191.84	7.490 (4.541)	0.14 x 10 (5.33 x 10^{-2})	-243.113 (-270.061)	4.787 (1.836)	83.840 (89.651)
	191.84-245.38	70.604 (61.296)	1.01 x 10^{7} (5.08 x 10^{5})	-115.039 (-139.908)	66.496 (57.184)	123.345 (126.323)
	245.38-370.60	63.120 (53.453)	1.18 x 10^{5} (6.37 x 10^{3})	-153.336 (-177.605)	58.322 (48.652)	146.805 (151.139)
	370.60-476.10	40.988 (29.425)	1.320 x 10^{2} (1.320 x 10)	-211.340 (-230.486)	35.254 (23.687)	181.020 (182.658)
	476.10-640.02	79.003 (63.555)	9.30 x 10^{3} (7.73 x 10^{2})	-177.686 (-198.371)	71.929 (56.476)	223.106 (225.252)

Figure 3 shows the DSC curves of DAP and VAR, very strong and sharp endothermic peaks appear at 181.75 °C and 218.93 °C which may be attributed to the melting of DAP and VAR, respectively.

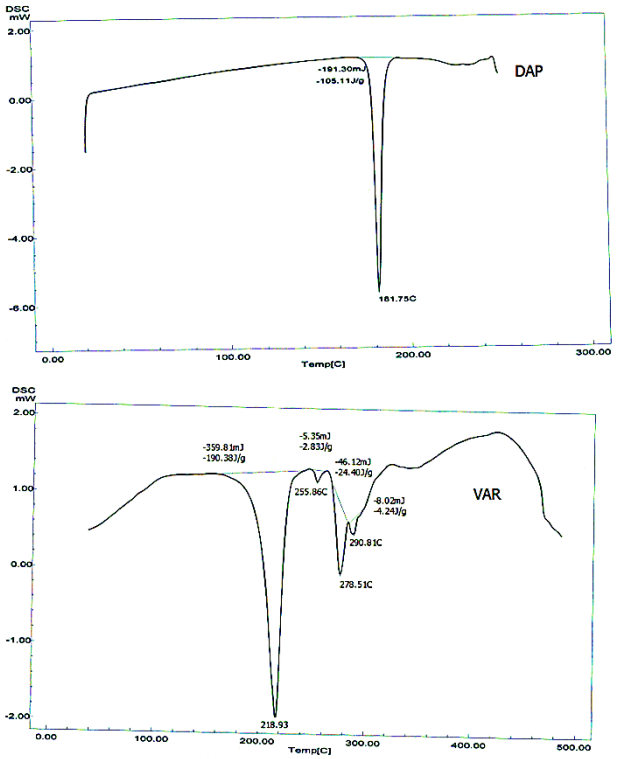

Figure 3. DSC curves of DAP and VAR.

The purity values of DAP and VAR are found to be 99.97% and 99.95%, respectively. These values are very good when compared with the purity of the used drugs 99.92% and 99.94% for DAP and VAR, respectively. DSC curve of VAR shows two weak endothermic peaks at 255.86 °C and 290.81 °C and medium endothermic peak at 278.51 °C. The results are listed in Table 2.

Applications of thermal analysis on Joypox and Rectivard tablets

Figure 4 A shows the DTA curves of Joypox and Rectivard tablets, the dosage forms of DAP and VAR, respectively. The endothermic and exothermic peaks of DAP and VAR (Figure 1) are different in their values and shapes in comparison with the endothermic and exothermic peaks of Joypox and Rectivard tablets. An endothermic peak appears at 148.25 °C and a broad endothermic peak between 156.61 °C and 280.67 °C in DTA curves of Joypox and Rectivard tablets which may be attributed to the melting their active ingredients, DAP and VAR, respectively. These values are smaller than that of pure drugs 183.57 °C and 218.38 °C for DAP and VAR, respectively according to the presence of excipients in tablets which act as impurities and decreasing the melting point of the drugs. Also the strong and sharp exothermic peaks at 553.70 °C and 577.81 °C for DAP and VAR appear as very weak and broad peaks between 390.26 °C and 724.97 °C and between 419.35 °C and 678.89 °C in case of Joypox and Rectivard tablets, respectively. Figure 4 B shows the DTA curves of excipients. The results are listed in Table 2.

Table 2. Melting point and degree of purity of DAP and VAR and endothermic and exothermic peaks of inactive ingredients.

Drug	Melting point (°C)				Degree of purity (%)	
	DTA method	Melting point apparatus	DSC Method	Literature[25]	DSC	Reported
DAP	183.57	180.34	181.75	179.00-183.00	99.97	99.92
VAR	218.38	218.22	218.93	218.00	99.95	99.94
Endothermic and exothermic peaks of inactive ingredients						
Peak (°C)	**Lactose monohydrate**	**Starch**	**Magnesium stearate**	**Microcrystalline cellulose**	**Povidone**	
Endothermic	149.97,215.42	67.97	375.07	325.30	65.95	
Exothermic	358.42,530.52	327.32, broad peak between 338.63 and 613.74	396.67,418.70,458.59	357.62, broad peak at 533.70	428.31, broad peak between 442.85 and 634.74	

Figure 5 shows the DSC curves of Joypox and Rectivard tablets, weak and sharp endothermic peaks at 144.62 °C and 187.68 °C which may be attributed to melting of DAP and VAR in tablets, respectively. These melting points values are lesser than the listed values of DAP and VAR in Table 2. The decreasing in melting points values is due to the presence of excipients. Other broad and weak endothermic peaks appear at 192.21 °C (Joypox tablets), 66.99 °C and 217.24 °C (Rectivard tablets).

Conclusion

This paper is the first attempt to study the thermal behavior of DAP and VAR using thermal analysis and differential scanning calorimetry (DSC) techniques. The results indicate to the stability; endothermic or exothermic processes during the degradation ad the activation energy needed for each stage for decomposition. The melting points values obtained by DTA and DSC refer to the precision of these techniques comparing with the reported methods. This justifies the use of these techniques for the identification of for pharmaceutical compounds through measuring the melting points values. DSC technique can be used to determine purity of drugs giving compatible results with the results obtained using the reported methods. This

work reveals the importance of the thermal analysis and DSC techniques for the quality control of drugs.

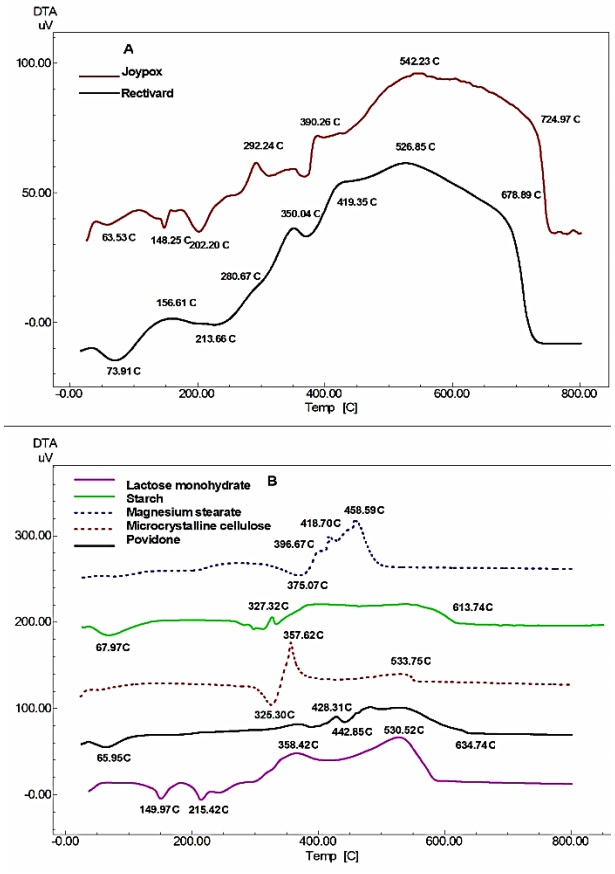

Figure 4. DTA curves of Joypox and Rectivard tablets (A) and some inactive ingredients (B).

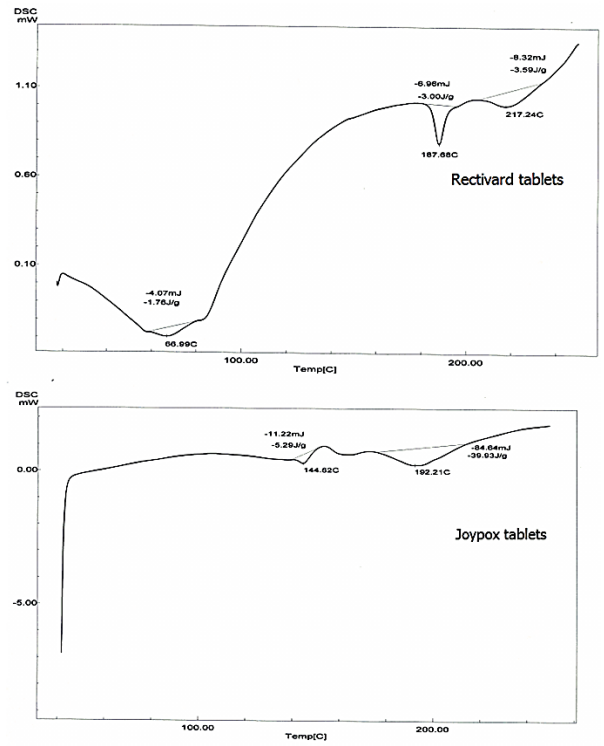

Figure 5. DSC curves of Joypox and Rectivard tablets.

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Ethical Issues

Not applicable.

Conflict of Interest

The authors report no conflicts of interest.

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