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Research Article

Thermoanalytical Investigation of Some Sulfone-Containing Drugs

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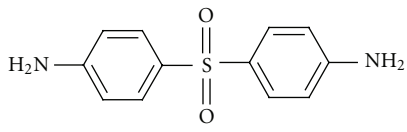
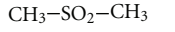
The thermal behavior of some sulfone-containing drugs, namely, dapsone (DDS), dimethylsulfone (MSM), and topiramate (TOP) in drug substances, and products were investigated using different thermal techniques. These include thermogravimetry (TGA), derivative thermogravimetry (DTG), differential thermal analysis (DTA), and differential scanning calorimetry (DSC). The thermogravimetric data allowed the determination of the kinetic parameters: activation energy (E_a), frequency factor (A), and reaction order (n). The thermal degradation of dapsone and topiramate was followed a first-order kinetic behavior. The calculated data evidenced a zero-order kinetic for dimethylsulfone. The relative thermal stabilities of the studied drugs have been evaluated and follow the order DDS > TOP > MSM. The purity was determined using DSC for the studied compounds, in drug substances and products. The results were in agreement with the recommended pharmacopoeia and manufacturer methods. DSC curves obtained from the tablets suggest compatibility between the drugs, excipients and/or coformulated drugs. The fragmentation pathway of dapsone with mass spectrometry was taken as example, to correlate the thermal decomposition with the resulted MS-EI. The decomposition modes were investigated, and the possible fragmentation pathways were suggested by mass spectrometry.

1. Introduction

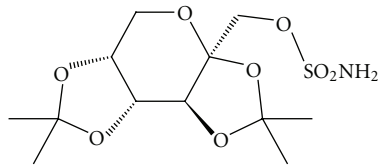
Dapsone (DDS). It is antibacterial drug used in the treatment of *Mycobacterium leprae* infection (leprosy), and malaria [1, 2]. It is official in BP and USP [3, 4]:



Dimethyl Sulfone (MSM). It is used as anti-inflammatory agent [5, 6] and in combination with glucosamine and chondroitin to treat or prevent osteoarthritis [7, 8]:



Topiramate (TOP). It is antiepileptic drug [9]. It is official in USP [4]:



Different analytical methods were reported for the assay of DDS in dosage forms and in biological fluids, including spectroscopy [10–21], electrochemical methods [22, 23], and chromatography [24–28]. In literature two GC methods were reported for determination of dimethyl sulfone [29, 30]. Topiramate has no ultraviolet, visible, or fluorescence absorption, and available methods for analysis of the drug in

biological fluids and pharmaceutical dosage formulation consisted of gas chromatography (GC) coupled with flame ionization (FID) or nitrogen phosphorous detection (NPD) [31–33] and fluorescence polarization immunoassay [34]. HPLC methods, including ionic chromatography, or using refractive index (RI), chemiluminescent nitrogen, or MS detector are described [35–37]. Analysis of the drug in human plasma following derivatization with 9-fluorenylmethyl chloroformate (FMOC-Cl) or 4-chloro-7-nitrobenzofurazan (NBD-Cl) using fluorescence or UV detection has been reported [38–41].

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 substance is subjected to a controlled temperature program. These methods find widespread use in quality control of drugs, with a view to improvement of the final product and for the determination of drug quality via the technological parameters [42]. These techniques include thermogravimetry (TGA), derivative thermogravimetry (DTG), differential thermal analysis (DTA), and differential scanning calorimetric (DSC) methods. 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 [43]. TGA is commonly employed in research and testing to determine degradation temperatures, absorbed moisture content of materials, decomposition and kinetic parameters. Differential thermal analysis (DTA) is a thermoanalytical technique, in which the temperature between the material under study and an inert reference (ΔT) is measured as a function of temperature (T), while the substance and reference material are subjected to temperature program [44]. A plot of ΔT against time or temperature is called DTA curve or thermogram. Changes in the sample, either exothermic or endothermic, can be detected relative to the inert reference. DTA curve can be used only as a finger print for identification purposes but usually the applications of this method are the determination of phase diagrams, heat change measurements, and decomposition in various atmospheres [45, 46]. Differential scanning calorimetry (DSC) is a thermoanalytical 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 analytical tool of great importance for the identification and purity testing of active drugs, yielding results rapidly and efficiently [47]. It is also applied for the quality control of raw materials used in pharmaceutical products [48].

Mass spectrometry is used to elucidate the structure of compounds. The compound is ionized and fragmented using the electron spray ionization technique. The term "decomposition" or "degradation" signifies the breakdown of one or more constituents of the substance into simple atomic groups. The thermal decomposition of a solid may also involve physical transformation such as melting and sublimation, and these changes may exert a significant effect on the subsequent chemical reaction [49].

In modern analytical laboratory, there is always a need for rapid and significant methods for identification and purity determination of drugs. The determination of the melting point using DSC method has been satisfactorily used as a method of evaluating the degree of purity of a compounds.

In literature no references have been found for application of TGA/DTG, DTA, and DSC for thermal decomposition of DDS, MSM, and TOP in their drug substances and products. Therefore, the objective of this study was to investigate the thermal stability, kinetic parameters, and compatibility between the studied drugs and excipients and/or coformulated drugs.

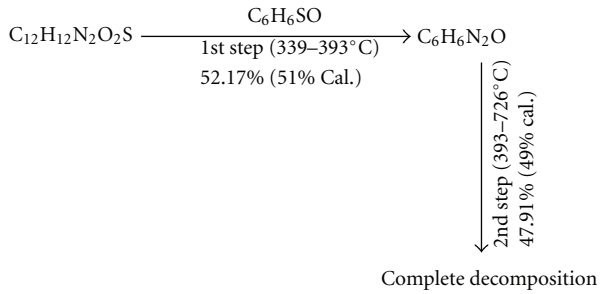
2. Experimental

2.1. Materials. Dapsone was kindly supplied from The Nile Company for Pharmaceuticals & Chemical Industries, Cairo; its purity was found to be 99.66% according to the official method [3]. Dapsone tablets labeled to contain 50 mg Dapsone/tablet—The Nile Company for pharmaceuticals & Chemical Industries, Cairo (batch no. 16226)—were purchased from local market. Dimethyl sulfone was obtained from Eva Pharma for Pharmaceuticals & Medical Applicances S.A.E. Co., Egypt; its purity was found to be 99.00% according to the manufacturer GC method. MSM tablets labeled to contain 1000 mg dimethyl sulfone/tablet (batch no: 702180) were purchased from local market. Genuphil tablets were obtained from Eva Pharma for Pharmaceuticals & Medical Applicances S.A.E. Co., Egypt. Each tablet contains MSM 375 mg, chondroitin sulphate 300 mg, and glucosamine sulphate 375 mg (batch no. 908458), purchased from the market. Topiramate was supplied from Delta Pharma, Egypt; its purity was found to be 99.00% according to the USP method [4]. Topamax 25 tablets labeled to contain 25 mg TOP/tablet Janssen—Cilag Co. (batch no. 9FS1Q00).

2.2. Instrumentation and Methods: Thermogravimetry, Derivative Thermogravimetry (TGA/DTG), and Differential Thermal Analysis (DTA). TGA/DTG, and DTA curves of drug substances were recorded using simultaneous Shimadzu thermogravimetric analyzer TGA-60 H with TA 60 software in 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 1000°C with a heating rate of 10°C/min. The sample mass was about 5 mg of the drug without any further treatment.

The kinetic parameters of decomposition such as activation energy (E_a), frequency factor (A), and reaction order (n) were calculated from TGA/DTG curves. Arrhenius equation [46] and the mathematical models of Horowitz and Metzger [47] and Coats and Redfern [50] were used for kinetic parameters determination.

Differential Scanning Salorimetry (DSC). The DSC curves of Dapsone, dimethyl sulfone and Topiramate were recorded using Shimadzu-DSC 50, in dynamic nitrogen atmosphere with a constant flow rate of 30 mL/min and heating rate of 2°C/min, up to temperature 200°C/min using a mass of about 2 mg of sample packed in platinum pan. DSC equipment was preliminarily calibrated with standard



Scheme 1: The suggested thermal degradation of Dapsone.

reference of indium. Ten tablets or capsules of the drug products of the studied drugs were homogenized, and accurately weighed amount equivalent to 2 mg of each drug substance was packed in the pan. Then the DSC curves were recorded.

Mass Spectrometry Electron Impact (MS-EI). Mass spectra of Dapsone were recorded using the Shimadzu-GC-MS-QP 1000 EX quadruple mass spectrometer with Electron Impact detector equipped with GC-MS data system.
Melting point instrumentas OptiMelt Automated Melting Point System, *SRS* Stanford Research System.

3. Results and Discussion

3.1. Thermal Characterization of the Investigated Compounds

Dapsone. The TGA/DTG curves of DDS presented in Figure 1 revealed two thermal decomposition stages and thermal stability up to 339°C. The first step shows a mass loss (Δm = 52.00%) in the interval of 339.12–393. 41°C, suggesting the release of C_6H_6SO molecule (51.00%, calc.). The second decomposition step shows a mass loss (Δm = 48.00%) in the temperature range 393. 41–726.86°C, suggesting the loss of $C_6H_6N_2O$ molecule (49.00%, calc.) by cleavage of amino group. The results are presented in Table 1.

The DTA curve (Figure 1) exhibits endothermic and exothermic peaks. The first endothermic peak at 185.12°C is due to the melting of the compound. The sharp endothermic peak at 368.18°C is attributed to the first decomposition corresponding to the first mass loss observed in TGA/DTG thermogram curves as shown in Figure 1.

The sharp exothermic peaks at (639.34–686°C) are due to the pyrolysis of the compound (Table 2). The suggested thermal decomposition pathway of Dapsone is summarized in Scheme 1.

Dimethyl Sulfone. TGA/DTG and DTA plots of MSM are represented in Figure 1. The thermal behavior of MSM shows complete mass loss after the melting point as shown in Figure 1. The DTG plot contained a large sharp peak, which abruptly returned to zero baseline this peak is characteristic of the zero-order kinetic process of evaporation. The mass loss was determined, and the results were stated in Table 1.

The DTA plot exhibited two endotherms corresponding to melting at 118°C, and the second endothermic peak suggests vapor pressure of the molten sample between the melting and boiling points.

Topiramate. The TGA/DTG and DTA curves are shown in Figure 1. The TGA/DTG curves show that TOP is thermally stable up to 151.32°C. TGA/DTG curves show three thermal decomposition steps. The first step shows mass losses 73.46% in temperature range (151.32–393.46°C) corresponding to formation of carbonaceous residue. The second and third steps show mass loss 25.265% in temperature range (393.46–722.43°C), due to pyrolysis of carbonaceous residue (Table 1).
The DTA curve presented in Figure 1 exhibits endothermic and exothermic peaks. The first peak at 130.53°C is due to melting of compound. The sharp endothermic peak at 154.07°C is attributed to the first decomposition corresponding to the first mass loss observed in TGA/DTG curves. The broad exothermic peaks at 181.07°C, 350.8°C are due to the pyrolysis of the compound (Table 1).

3.2. Kinetic Analysis.

The kinetics of the main thermal decomposition steps of DDS, TOP, and MSM were studied using the Arrhenius equation [46]. Computation of the kinetic parameters was based on the use of the Arrhenius equation applied to the solid-state reactions. The logarithmic form of the Arrhenius equation is

$$\ln K = \ln A - \frac{E}{\mathrm{RT}}. \tag{1}$$

The Arrhenius equation can be combined with the rate equation, which is written as

$$\frac{d\alpha}{dt} = K(T) f(\alpha) \tag{2}$$

Combining (1) and (2) gives the following relation:

$$\ln\left[\frac{\mathrm{d}\alpha/\mathrm{d}t}{f(\alpha)}\right] = \ln A - \frac{E}{\mathrm{RT}}, \tag{3}$$

where (α) is the decomposed fraction, ($\mathrm{d}\alpha/\mathrm{d}t$) is the rate of the reaction, $f(\alpha)$ is a function of the actual composition of the sample, K is the specific rate constant, (A) is the pre-exponential term, E is the activation energy, R : gas constant, and T : temperature in degrees Kelvin. Alfa (α) (the fraction reacted at a particular temperature) was calculated from the weight of the sample at temperature $T(W_t)$, the initial weight (Wi), and the final weight (W_f) using the following equation:

$$\alpha = \frac{Wi - W_T}{Wi - W_f}. \tag{4}$$

The differential form of (4) gives

$$\frac{d\alpha}{dt} = \frac{dw_t/dt}{Wi - W_f}. \tag{5}$$

The function (dw_t/dt) is obtained from the DTG data. Then, the rate of the reaction can be calculated directly. This value

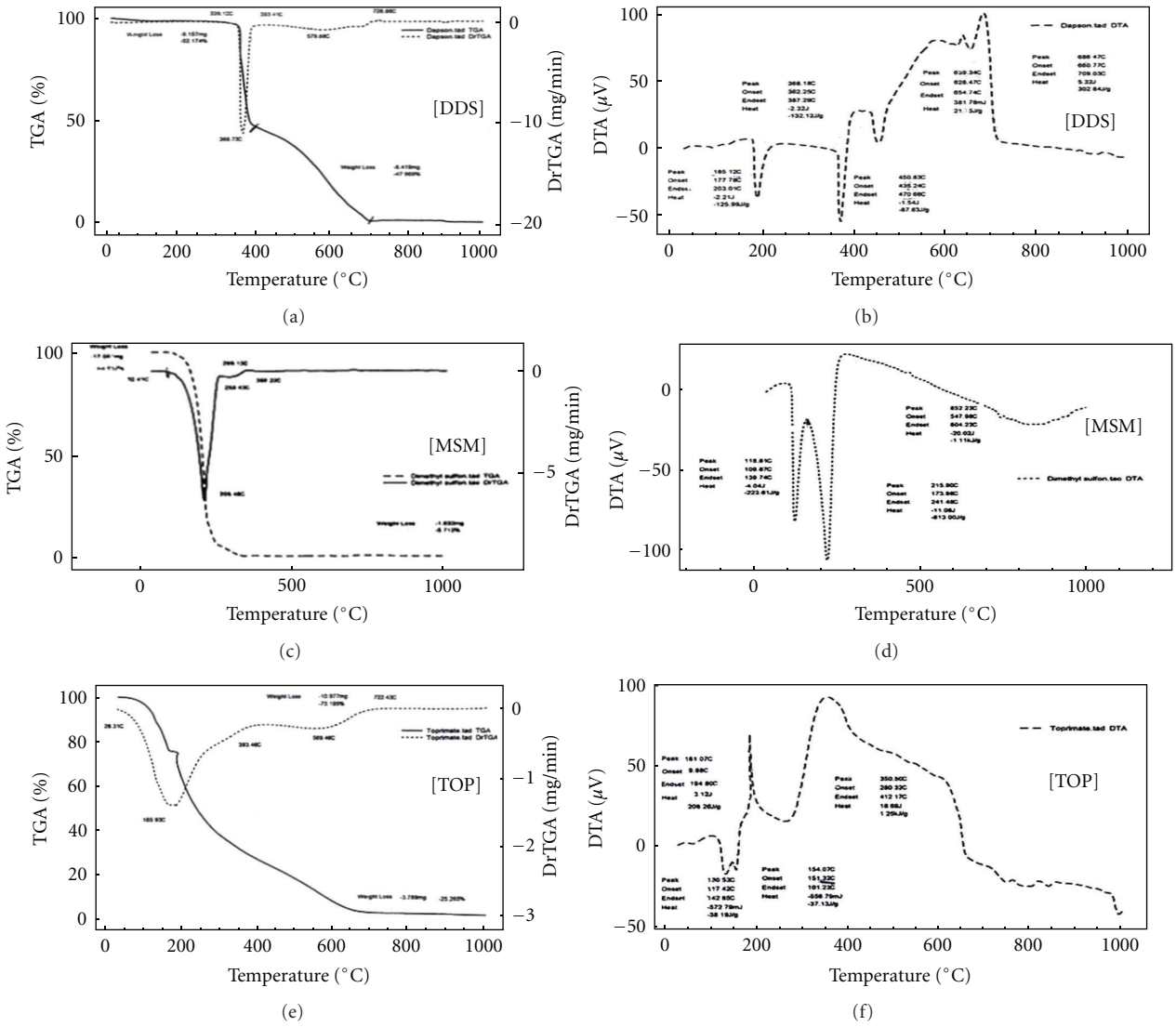


Figure 1: Thermal decomposition TGA/DTG and DTA for Dapsone, dimethyl sulfone, and Topiramate.

Table 1: Thermal decomposition data of TGA, DTG, and DTA curves of Dapsone, dimethyl sulfone, and Topiramate.

Drugs	TGA and DTG						DTA	
	1st reaction temperature			2nd reaction temperature			Endothermic peaks (°C)	Exothermic peaks (°C)
	Onset	End set	%wt loss	Onset	End set	%wt loss		
Dapsone	339	393.41	52.174	393.41	726	47.91	185.12 (refer to mp), 368.83, 639.34	686.34
Dimethyl sulfone	170	299.13	94.53	299.13	355	5.71	108.81 (refer to mp), 215.9	852.23
Topiramate	151	393.46	73.19	393.4	722.43	25.26	130.53 (refer to mp), 154.07	181.07, 350.80

of (dw_t/dt) obtained from (5) is substituted into (4), and finally, a plot of $\ln[(d\alpha/dt)/f(\alpha)]$ versus $1/T$ is constructed. The activation energy and the preexponential terms were calculated from the slope and the intercept, respectively [46].

The mathematical models used for identifying the term $f(\alpha)$, which refer to the order of reaction, were calculated according to reference table [51, 52]. The kinetic parameters obtained from the first decomposition step were activation energy (E_a), frequency factor (A), reaction order (n), and correlation coefficient (R). The calculated data evidenced a first-order kinetics behavior for DDS and TOP, with E_a value 485.83 KJ mol^{-1} and 93.78 KJ mol^{-1} respectively, while

Table 2: Kinetic parameters from the Arrhenius equation for Dapsone, Topiramate, and dimethyl sulfone.

Drug	Temperature range (°C)	Order of reaction	E_a (KJ moL^{-1})	ln A	R
Dapsone	339–393	1	485.87	88.255	0.9921
Topiramate	151–393	1	93.78	13.993	0.9957
Dimethyl sulfone	170–299	zero	51.006	11.815	0.9903

Table 3: Kinetic parameters obtained by the methods of Horowitz and Metzger (HM) and Coats and Redfern (CR) for Dapsone and Topiramate.

Drugs	Temperature range (°C)	E_a/kJ moL^{-1}		n		$A\cdot$Sec^{-1}
		HM	CR	HM	CR	CR
Dapsone	339–393	485	454	1	1	1.27×10^{32}
Topiramate	151–393	136.8	144.43	1	1	7.6×10^{8}

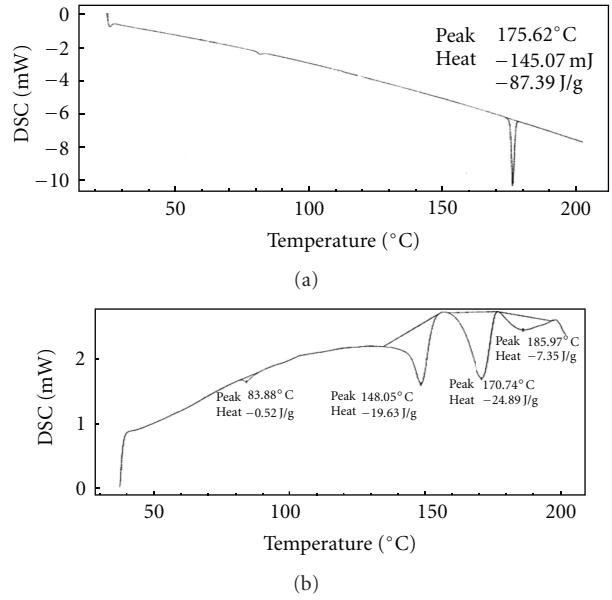


Figure 2: DSC profile of Dapsone drug substance (a), and Dapsone tablet (b).

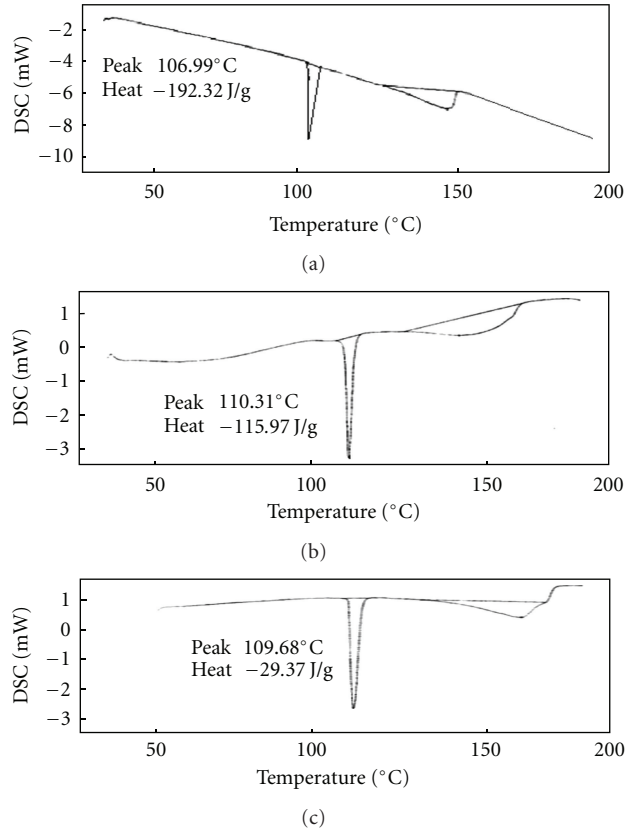


Figure 3: DSC profile of dimethyl sulfone drug substance (a), MSM tablet (b), and Genuphil tablet (c).

for MSM the data evidence zero-order E_a, with E_a value 51.003 KJ mol^{-1} (Table 2).

The kinetic studies of the main thermal decomposition steps of DDS and TOP were investigated also by using mathematical models of Horowitz and Metzger [47] and Coats-Redfern, respectively [50]. The calculated data evidenced also a first-order kinetics behavior for DDS with E_a values 485 kJ mol^{-1} (HM) and 456 KJ mol^{-1} (CR) and frequency factor 1.27×10^{32} Sec^{-1} (CR). Also the calculated data evidenced a first-order kinetics behavior for TOP with E_a values 136.76 kJ mol^{-1} (HM) and 144.43 KJ mol^{-1} (CR) and frequency factor 7.6×10^{8} Sec^{-1} (Table 3):

$$\log \cdot \left[\log \frac{W_f}{W_f - W}\right] = \frac{\theta \cdot E^*}{2.303\ RT_s^2} - \log 2.303. \quad (6)$$

where W is the mass loss at time t and W_f after total decomposition, R is the gas constant, T_s is the DTG peak temperature and $\theta = T - T_s$. A plot of log[log $W_f/(W_f - W)$] *versus* θ will give a straight line, and E_a was then calculated from the slope (Table 3):

$$\log\left(\frac{\log\left[W_f/W_f - W\right]}{T^2}\right) = \log\left[\frac{\mathrm{AR}}{\phi E^*}\left(1 - \frac{2\mathrm{RT}}{E^*}\right)\right] - \frac{E^*}{2.303\mathrm{RT}} \quad (7)$$

Table 4: Degree of purity and melting point of Dapsone, dimethyl sulfone, and Topiramate in drug substances by DSC, melting point apparatus, and pharmacopoeial and reported methods.

Drugs	Degree of purity%		Melting point (°C)		
	DSC*	Pharmacopoeial/reported	DSC	Mp apparatus	Pharmacopoeial/reported
Dapsone	99.66	100.29**	175.62	177	175–181
Dimethyl sulfone	99.73	99.36***	106.99	109	108–110
Topiramate	98.27	98.00****	122.41	125	122–126

*Mean of five instrumental run.
**Official BP 2010.
***Manufacturer GC method supplied by Eva Pharma, Egypt.
****Official USP 2011.

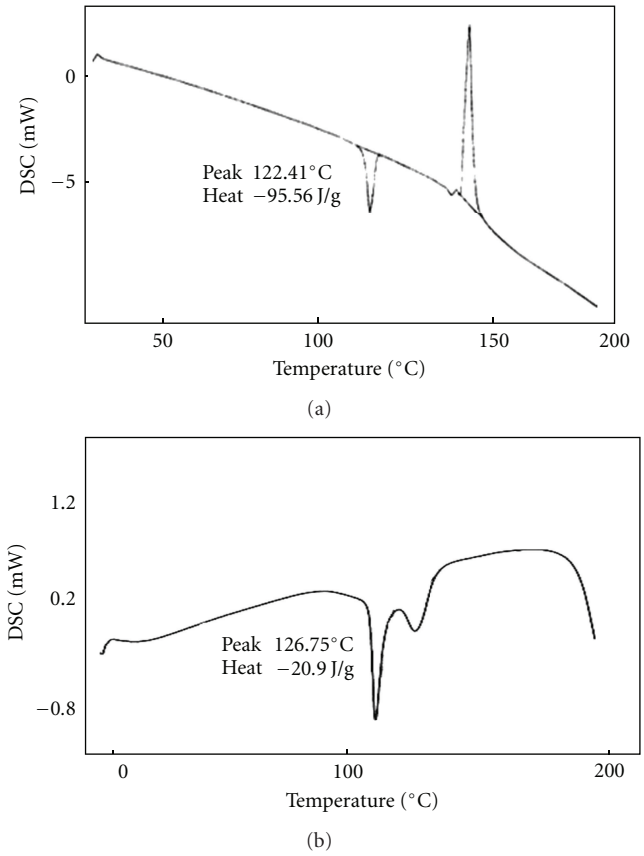
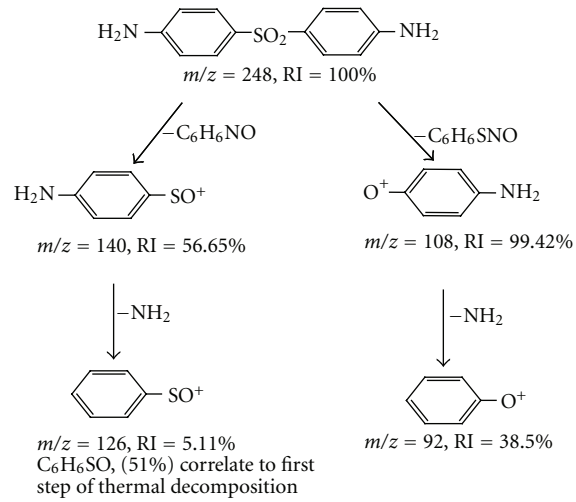


Figure 4: DSC profile of Topiramate drug substance (a), Topamax tablet (b).

ϕ is the heating rate (°C /min). Since $1-2RT/E^* \cong 1$, the plot of the left-hand side of (7) *versus* $1000/T$ will give a straight line. E_a was then calculated from the slope and the frequency factor (A) was obtained from the intercept (Table 3).

3.3. Correlation between the Mass Spectra and Thermal Behavior of Dapsone. Mass spectrometry is used to elucidate the structure of a compound. In mass spectrometry the compound is ionized and fragmented using the electron spray ionization technique, while for thermal analysis the term



Scheme 2: Mass spectral fragmentation pathways of Dapsone.

decomposition signifies the breakdown of one or more constituents of the substance into simpler atomic grouping. Dapsone has symmetrical molecule which upon decomposition gives main fragments, with m/z = 140 (RI = 56.17%), m/z = 108 (RI = 92.2%), and m/z = 126 (RI = 5.11%). Fragments at m/z = 248 (RI = 100%) represent the base peaks of DDS. The electron ionization mass spectrum of the fragmented Dapsone shows an abundance of C_6H_6SO (m/z = 126, 51%) molecule, suggesting that this is a major part of the decomposition lost in thermal reaction. The correlation was presented in Scheme 2.

3.4. Application of Differential Scanning Calorimetry for Purity Determination of Dapsone, Dimethyl Sulfone, and Topiramate in Drug Substances. The determination of purity is based on the assumption that impurities will depress that the melting point of a pure material whose melting is characterized by a melting point (T_0) and an enthalpy of fusion (ΔH_f). The melting transitions of a pure 100% crystalline material should be infinitely sharp, but impurities or defects in the crystal structure will broaden the melting range and lower the final melting point to a temperature lower than T_0 [53]. Purity determination is officially listed

Table 5: Application of the proposed DSC method for determination of the claimed amount of Dapsone, dimethyl sulfone, and Topiramate in their pharmaceutical formulations.

Dosage forms	Claimed amount* % by the proposed DSC	Claimed amount % by pharmacopoeial and/or reported methods
Dapsone (50 mg of Dapsone/tab)	91.25	96.28**
MSM (100 mg MSM/tab)	95.36	94.56***
Genuphil tablet (375 mg MSM/tab)	96.33	—
Topamax (25 mg TOP/tab)	93.54	94.26****

* Mean of five instrumental run.
** Official BP 2010.
*** Manufacturer GC method supplied by Eva Pharma, Egypt.
**** Official USP 2012.

in the British and United States Pharmacopoeias in general chapter on thermal analysis [14, 15]. The effects of impurities on T_0 of DDS, MSM, and TOP were determined by DSC method based on the van't Hoff equation:

$$T_s = T_o - RT_0^2 \cdot \frac{1}{\Delta H_f} \cdot F, \tag{8}$$

where T_s is the sample peak at temperature (K), T_0 is the melting point of pure component (K), R is the gas constant, X is the concentration of impurity (grams fraction), ΔH_f is heat of fusion of pure component (J mg^{-1}), and F is the fraction of sample melted at T_s.

The DSC curves allowed determination of the melting points and the degrees of purity of the drugs. The results obtained by the official volumetric method, manufacturer GC method, and official HPLC-RI method for DDS, MSM, and TOP, respectively, afforded values similar to those found by DSC (Table 4). Comparison of the data on the studied drugs revealed the importance of the DSC technique for quality control of bioactive drugs. The melting points obtained by DSC revealed the precision of the technique in yielding these thermal parameters, as the RSD less than 2% ($n = 5$). This justifies the use of DSC as a routine technique for identification of drugs designed for pharmaceutical use, through the melting point.

3.5. Application of Differential Scanning Calorimetry for Determination of Dapsone, Dimethyl Sulfone, and Topiramate in Their Pharmaceutical Formulations. DSC curves of DDS in drug substance and product were presented in Figure 2. Dapsone tablet (Figure 2) exhibited two shallow broaden endothermic peaks, suggesting an interaction between the drug and excipients but not necessary corresponding to incompatibility. This was attributed to drug dissolution in the melted excipient [53]. The DSC curves of MSM raw material, MSM tablet, and Genuphil tablet are presented in Figure 3. The data suggested compatibility between the drug and excipients and/or coformulated drugs. For TOP the DSC curves of raw material and Topamax tablet suggested compatibility between the drug and excipients as shown in Figure 4 this means that the excipients increase the stability of the drug. The results are stated in Table 5. The RSD is less than 5% ($n = 5$).

4. Conclusions

The thermal stability of DDS, MSM, and TOP using different thermal techniques (TGA/DTG, DTA, and DSC) was studied. The kinetic studies of DDS and TOP showed a thermal behavior characteristic to first order while zero for MSM. The thermal stability of the studied drugs followed the order DDS > TOP > MSM according to E_a. The correlation between mass spectra and thermal behavior of DDS revealed correlation between the two techniques. The electron ionization mass spectrum of the fragmented Dapsone shows an abundance of C_6H_6SO molecule, suggesting that this is a major part of the decomposition lost in thermal reaction. The DSC method is not always appropriate for purity determination of pharmaceuticals. This method describes the determination of purity of materials greater than 98.5 mole percent purity using differential scanning calorimetry and the van't Hoff equation. The DSC data showed compatibility between the studied drugs and excipients and/or coformulated drugs. It provides a rapid method for purity determination attending a value between 98 and 102%, which is in agreement with the official pharmacopoeia. The simplicity, speed, and low operational costs of thermal analysis of pharmaceuticals justify its application in quality control.

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