*Advanced Pharmaceutical Bulletin,* **2013**, 3(2), 419-424
doi: http://dx.doi.org/10.5681/apb.2013.067
http://apb.tbzmed.ac.ir/

# Thermal Analysis of Some Antidiabetic Pharmaceutical Compounds

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**ARTICLEINFO**

***Article Type:***
Research Article

***Article History:***
Received: 20 April 2013
Revised: 20 May 2013
Accepted: 2 June 2013
ePublished: 20 August 2013

***Keywords:***
Antidiabetics
Thermal analysis
Decomposition
Activation energy

**ABSTRACT**

***Purpose:*** Thermal behavior of some antidiabetic drugs such as pioglitazone hydrochloride (PTZ), rosiglitazone maleate (RGZ), glibenclamide (GBD) and glimepiride (GMP) has been studied. ***Methods:*** Thermogravimetric analysis (TGA), derivative thermogravimetry (DTG) and differential thermal analysis (DTA) techniques were used to study the thermal behavior of the drugs under investigation. ***Results:*** Thermal analysis technique was used to obtain quality control parameters such as melting point 193.13 °C, 122.42 °C, 173.75 °C and 208 °C for PTZ, RGZ, GBD and GMP, respectively. The values of melting point of gave satisfactory results in comparison to that obtained by using the official method. Non-isothermal methods were employed to determine the activation energy values of the first stage of thermal decomposition. Comparison of the activation energy values suggests the following sequence of thermal stability: GMP > GBD > RGZ > PTZ. ***Conclusion:*** The results obtained are useful for the identification of these compounds and permitted interpretations concerning their thermal decomposition. Thermal stability of pharmaceutical compounds can be studied and compared by using thermal analysis techniques.



## Introduction

Thermal analysis is a technique in which a physical property of a substance and/or its reaction products is measured as a function of temperature. Thermal analysis can measure weight loss on heating, melting points, heat and energy transitions and change in the substance form. Thermal analysis techniques are widely used in the pharmaceutical sciences for the characterization and quality control of drugs, stability, drug-excipient interactions and purity studies of raw materials and pharmaceutical products.[1-5]

Several methods have been reported for the determination of the studied drugs including chromatographic,[6-9] electrochemical,[10] and titrimetric methods.[11,12] The use of thermal analysis for antidiabetic drugs has been very limited; compatibilities of some commonly used pharmaceutical excipients with glimepiride and glibenclamide have been described.[13,14] Therefore, the main objective of this study is to investigate and compare the thermal behavior of some antidiabetic drugs such as PTZ, RGZ, GBD and GMP using the TGA, DTG and DTA techniques.

PTZ is an oral antidiabetic agent used in the treatment of type 2 diabetes. After administration, PTZ decreases insulin resistance in the periphery and liver resulting in increased insulin dependent glucose disposal and decreased hepatic glucose output.[15,16] RGZ is a thiazolidinedione antihyperglycemic agent that works by increasing insulin sensitivity in target tissues, as well as decreasing hepatic gluconeogenesis.[17] Oliveira et al studied isothermal thermogravimetric studies and compatibility between GBD and some pharmaceutical excipients using thermoanalytical techniques (TGA/DSC).[13] Cides et al studied the thermal behavior, compatibility study and decomposition kinetics of glimepiride by using isothermal and non-isothermal methods. The activation energy values are 123 and 150 KJ.mol$^{-1}$ using isothermal method and Onawa method, respectively.[14]

GBD and GMP are the potent second generation oral sulfonylurea antihyperglycemic agents that widely used for the treatment of type 2 diabetes mellitus.[18,19]

## Materials and methods

Pioglitazone hydrochloride and rosiglitazone maleate were obtained from Unipharma and Apex Pharmaceutical Company, Egypt, respectively; glibenclamide and glimepiride were supplied from Aventis Pharmaceutical Company, Egypt. All the used drugs have high purity (more than 99%).

### *Methods*

Thermogravimetric analysis, derivative thermogravimetry and differential thermal analysis measurements were made by using simultaneous DTA-TGA thermal analyzer apparatus (Shimadzu DTG-

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60H). The weight of samples is ranging from 4 to about 7 mg, using a platinum pan. Measurements were carried out from ambient to 900 °C in dynamic nitrogen atmosphere with the flow rate of 30 ml $min^{-1}$ and heating rate of 10 °C $min^{-1}$.

The activation energies of the used drugs for the first stage of decomposition were obtained from TGA curves by using Coats-Redren method,[20] and Horowitz-Metzger method.[21]

### *Coats-Redfern method*

The Coats-Redfern method equation can be represented as follows:

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

Where ϕ was the heating rate. 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 (A) was obtained from the intercept.

### *Horowitz and Metzger method*

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, $T_s$ 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.

## Results and Discussion

### *Thermal analysis behavior of PTZ*

The TGA, DTG and DTA curves of PTZ are shown in Figure 1. The DTG curve shows four stages of decomposition: At the first stage (145-225.9 °C); PTZ exhibits a weight loss of 9.53% due to the loss of HCl molecule. A weight loss of 57.09% observed between 225.9 °C and 327.73 °C which may be attributed to the loss of $C_{10}H_8NO_3S$. Beyond 389.34 °C, the drug decomposed in two stages due to the loss of $C_4H_9$ at 389.34-468 °C (weight loss of 14.71%) and the loss of $C_5H_3N$ at 468-551.55 °C (weight loss of 19.47%).

The DTA curve (Figure 1) shows a small endothermic peak at 193.13 °C due to the melting of PTZ which is acceptable to the values of the reported melting temperature,[22] and the melting temperature that determined by melting point apparatus (Table 1). An exothermic peak is observed at 270.75 °C corresponding to the second decomposition stage. Another abroad endothermic peak appears between 327.73 °C and 389.34 °C. Two sharp exothermic peaks are observed at 444.47 °C and 498.20 °C corresponding to the third and fourth decomposition stages in the DTG curve, respectively. The results obtained from TGA, DTG and DTA indicate that PTZ melts with decomposition. Thermal degradation pattern of PTZ was shown in Figure 2.

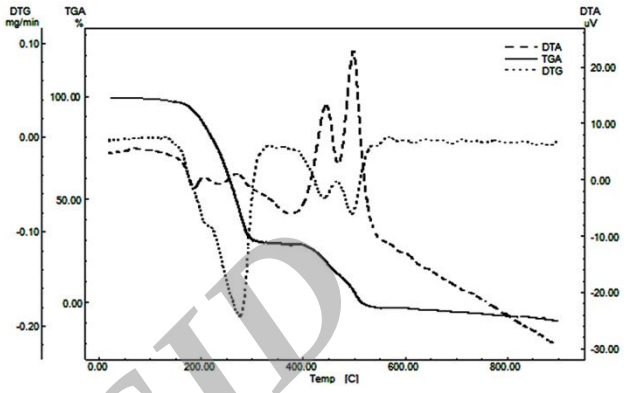


**Figure 1.** Thermal analysis curves (TGA, DTG and DTA) of PTZ.

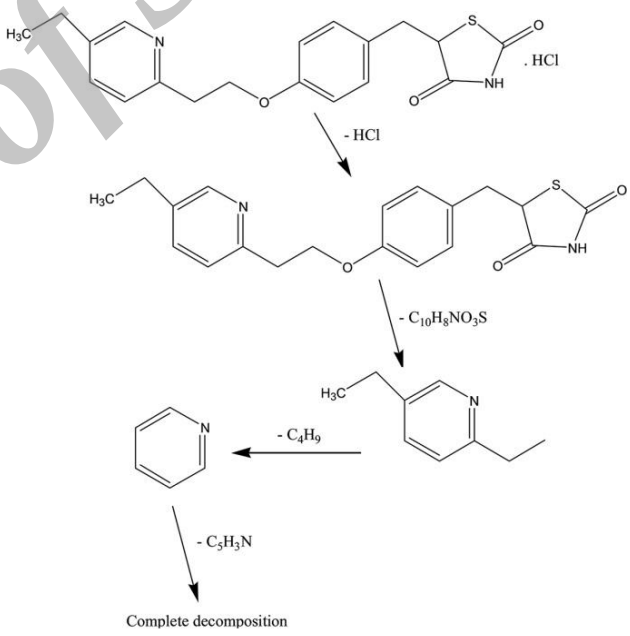


**Figure 2.** Thermal degradation pattern of PTZ.

### *Thermal analysis behavior of RGZ*

Figure 3 represents TGA, DTG and DTA curves of RGZ. The TGA curve shows four stages of decomposition. The DTG curve represents the stages of decomposition: the first one begins at 150.61 °C and ends at 231.43 °C with a mass loss of 24.50% due to the loss of $C_4H_4O_4$ molecule, the second stage between 231.43 °C and 317 °C shows weight loss of 24.50% due to the loss of $C_3H_2NO_2S$. RGZ continues to decompose in a third stage (317-481°C) showing a mass loss of 22.39% due to the loss of $C_7H_6O$ and fourth and last stage (481-644.58 °C) with a mass loss of 28.51% which may be ascribed to the loss of $C_8H_{11}N_2$.

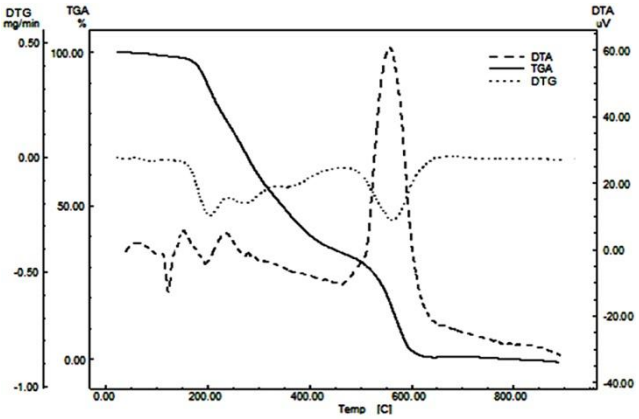


**Figure 3.** Thermal analysis curves (TGA, DTG and DTA) of RGZ.

The DTA curve in Figure 3 shows an endothermic peak at 122.42 °C attributed to the melting of the compound which agrees to the reported melting temperature,[22] and the melting temperature that determined by melting point apparatus. The results were shown in Table 1. One endothermic peak is found at 192.75 °C corresponding to the first decomposition stage. Broad endothermic peak presented from 231.43 °C to 481 °C which corresponds to the second and third stages of decomposition. A very strong and sharp exothermic peak is showed at 556.49 °C which may be attributed to the last decomposition stage. Thermal degradation pattern of RGZ was shown in Figure 4.

**Table 1.** The melting points values and the activation energies for the first stage of decomposition of PTZ, RGZ, GBD and GMP.

| Drug | Melting point (°C) | | | Activation energy E* (KJ.mol$^{-1}$) | |
|---|---|---|---|---|---|
| | DTA Method | Apparatus | Literature [22] | Coats-Redfern method | Horowitz-Metzger method |
| PTZ | 193.13 | 194.00 | 193.00-194.00 | 77.44 | 88.19 |
| RGZ | 122.42 | 123.00 | 122.00-123.0 | 102.29 | 111.72 |
| GBD | 173.75 | 174.00 | 172.00-174.00 | 114.23 | 126.73 |
| GMP | 208.00 | 206.00 | 207.00 | 125.79 | 142.62 |

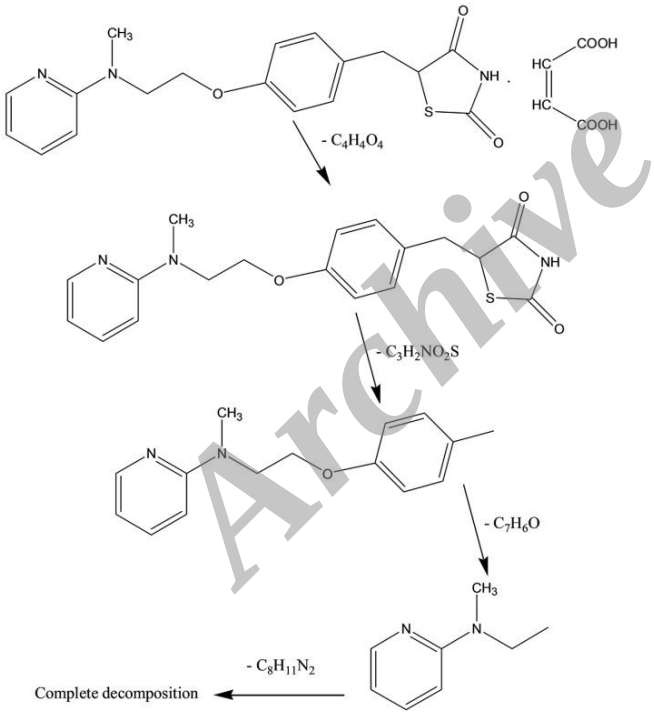


**Figure 4.** Thermal degradation pattern of RGZ.

### *Thermal analysis behavior of GBD*

The TGA, DTG and DTA curves in Figure 5 show that GBD is thermally stable up to 185 °C. The TGA and DTG curves indicate mass losses in three well defined stages between 185 °C and 677.53 °C. The mass loss 28.54% for the first stage (185-286.60 °C) suggests the elimination of $C_7H_{13}N_2O$. The second stage of decomposition (286.60-392.36 °C) involves a loss in mass of 43.13% which corresponds to the loss of $C_{10}H_{11}NClO_2$ and the third and final stage (392.36-677.53 °C) involves a mass loss of 28.34% which corresponds to the loss of $C_6H_4SO_2$.

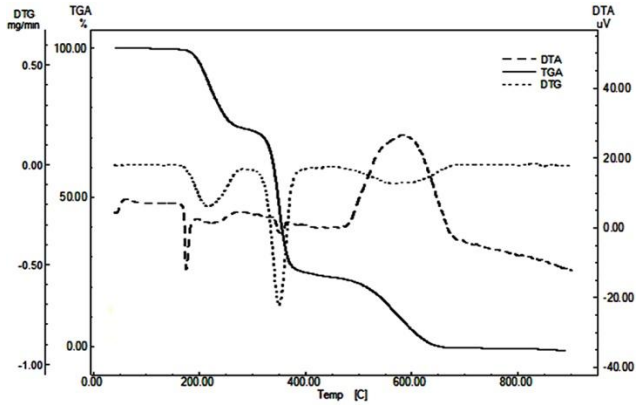


**Figure 5.** Thermal analysis curves (TGA, DTG and DTA) of GBD.

The DTA curve shows a sharp endothermic peak at 173.75 °C due to the melting of the GBD which is in agreement with the values obtained from literature,[22] and by using melting apparatus (Table 1); this peak is followed by a small and flattened endothermic peak from 196 °C to 286.60 °C which corresponds to the first decomposition stage. At 350.81 °C the DTA curve shows a small endothermic peak which corresponds to the second decomposition stage and a strong and broad exothermic peak at 580 °C which is due to the last decomposition stage of the drug. Thermal degradation pattern of GBD was shown in Figure 6.

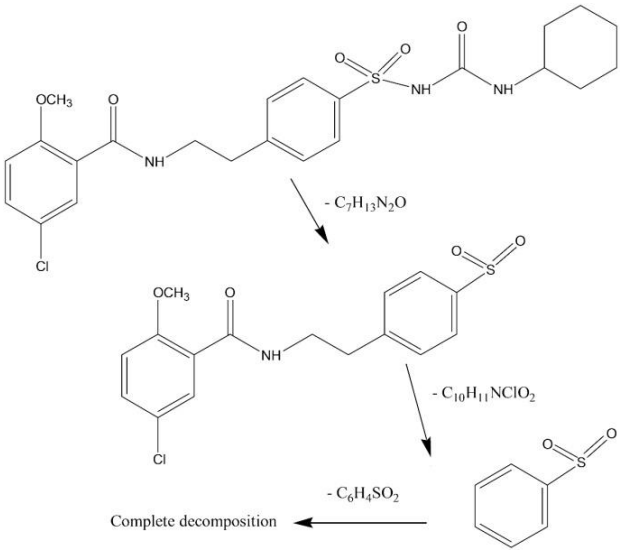


**Figure 6.** Thermal degradation pattern of GBD.

### *Thermal analysis behavior of GMP*

The TGA and DTG curves in Figure 7 show that GMP is thermally stable up to about 198 °C and then decomposes in the first stage up to 269.31 °C with a mass loss of 31.75% which suggests the loss of $C_8H_{15}N_2O$. GMP continues to decompose from 269.31 °C to 369 °C in the second stage of decomposition showing a mass loss of 39.66% due to the loss of $C_{10}H_{15}N_2O_2$ and the third and last stage in the temperature range of 369-690 °C (28.54%) is ascribed to the loss of $C_6H_4SO_2$.

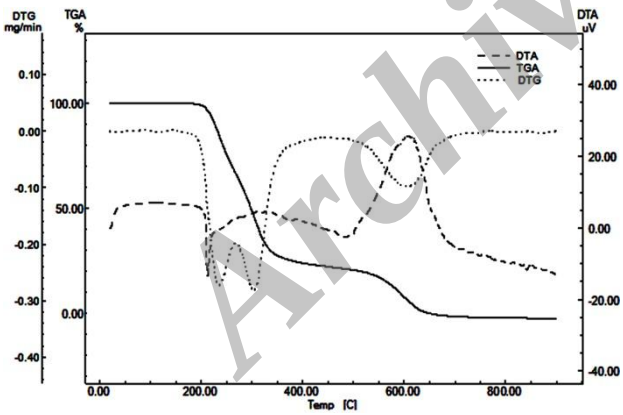


**Figure 7.** Thermal analysis curves (TGA, DTG and DTA) of GMP.

The DTA curve of GMP (Figure 7) shows a sharp endothermic peak at 208 °C that corresponds to melting followed by a broad flat exothermic peak between 220 °C and 480 °C which is corresponding to the first and second stages of decomposition of GMP followed by a strong and broad exothermic peak at 607 °C corresponding to the third decomposition stage of GMP. Thermal degradation pattern of GMP was shown in Figure 8.

The previous results show that PTZ, RGZ, GBD and GMP start to decompose at 145 °C, 150.61 °C, 185 °C and 198 °C, respectively. These results suggest increasing thermal stability in the same order. Kinetic studies were conducted to investigate these results through calculation and comparison of the activation energies obtained from the first stage of decomposition of these drugs.

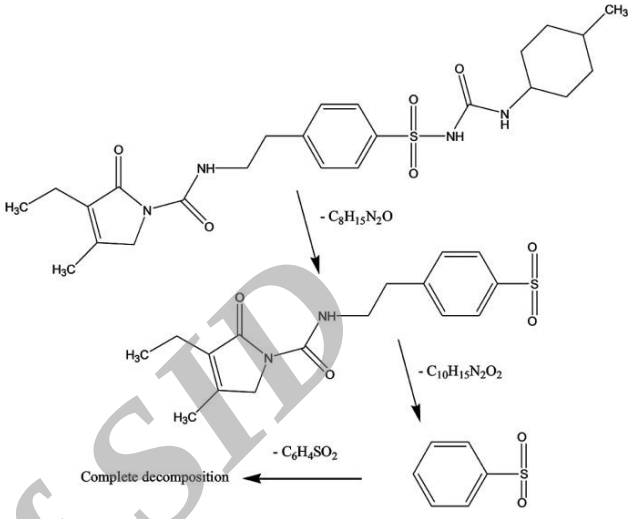


**Figure 8.** Thermal degradation pattern of GMP.

### *Determination of* activation energies

For the first order kinetic process, the activation energy ($E^*$) values for the first stages of decomposition of PTZ, RGZ, GBD and GMP were determined by using Coats-Redfern and Horowitz-Metzger methods. The results are shown in Figure 9 and Figure 10. The activation energy values of GMP are 123 and 150 KJ.mol$^{-1}$ using isothermal method and Ozawa's method, respectively.[14] These results are in agreement with the values obtained from Coats-Redfern and Horowitz-Metzger methods, and this is an important experimental finding. The results were listed in Table 1. It is clear that the obtained values of activation energies of the used drugs are in reasonably good agreement. The activation energies obtained for the first stage of decomposition of these drugs show different values, suggesting the following sequence of thermal stability: GMP > GBD > RGZ > PTZ.

## Conclusion

Thermal analysis methods are widely used in the fields of pharmaceutical sciences. The TGA, DTG and DTA curves permitted interpretations of some antidiabetic agents such as PTZ, RGZ, GBD and GMP concerning their thermal decomposition. Thermal stability of pharmaceutical compounds can be studied and compared by using thermal analysis techniques. The results justify the use of DTA as a routine technique for the identification of these drugs through the melting point. Kinetic results demonstrated differences in thermal stability between the four drugs and suggested the following sequence of stability: GMP > GBD > RGZ > PTZ.

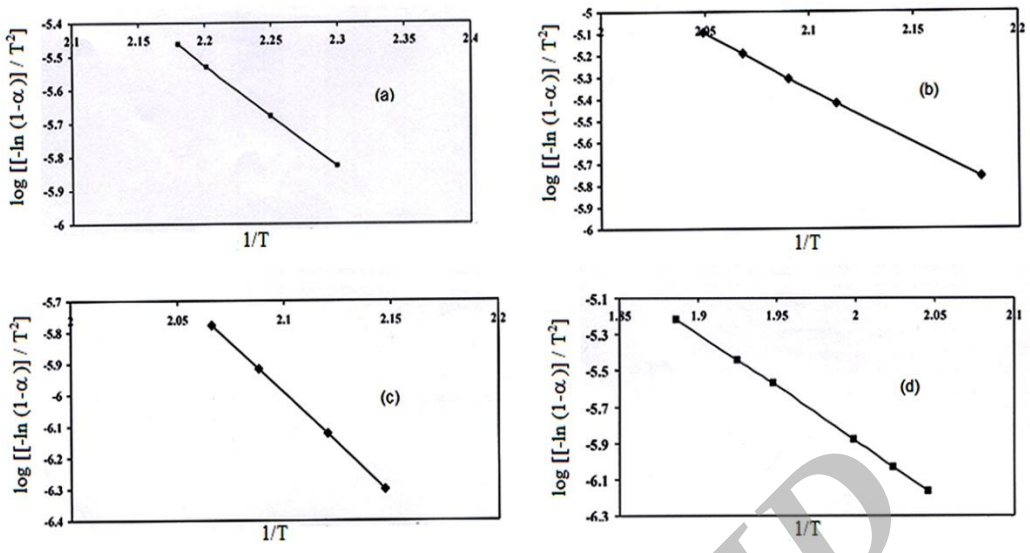


**Figure 9.** Coats-Redfern plots of PTZ (a), RGZ (b), GBD (c) and GMP (d), α = W / $W_f$.

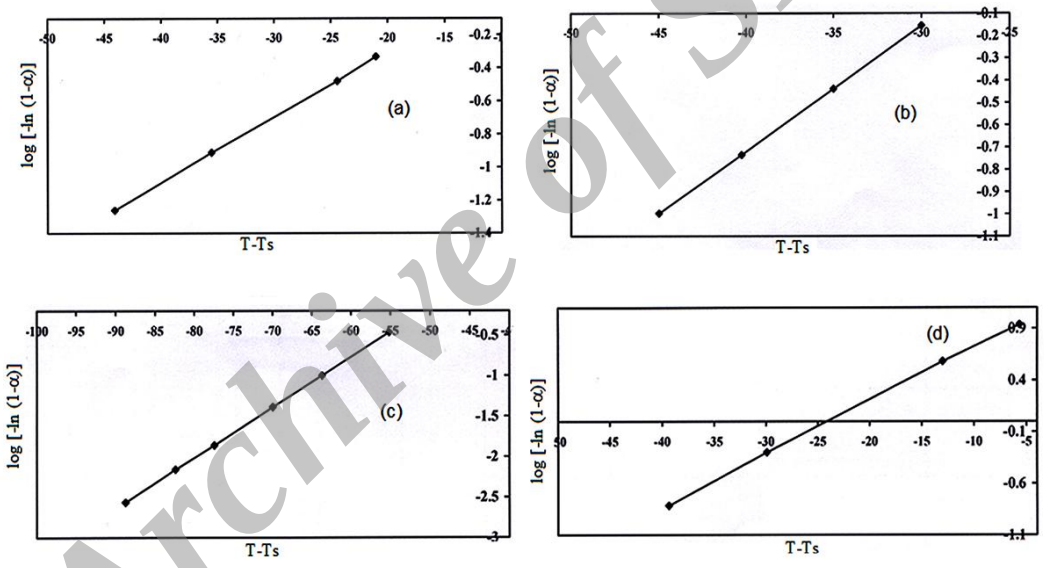


**Figure 10.** Horowitz-Metzger plots of PTZ (a), RGZ (b), GBD (c) and GMP (d), α = W / $W_f$.



## Conflict of Interest

The authors report no conflicts of interest.

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