RESEARCH PAPER

Thermal Hazard Evaluation of Tenofovir Disoproxil Fumarate Using Differential Scanning Calorimetry

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ABSTRACT

Thermal hazard evaluation of active pharmaceutical ingredients is essential for ensuring safe processing, storage, and scale-up in pharmaceutical manufacturing. In the present study, the thermal decomposition behavior and hazard potential of Tenofovir Disoproxil Fumarate (TDF) were systematically investigated using Differential Scanning Calorimetry (DSC) under both dynamic and isothermal conditions. Dynamic DSC experiments were carried out at heating rates of 1, 3, 5, 7, and 9 °C min^{-1} to determine the thermal transition characteristics, including melting behavior, onset temperature, and exothermic decomposition profile. The activation energy obtained from Arrhenius analysis under dynamic conditions was found to be 155.34 kJ mol^{-1}, indicating a thermally activated decomposition process. Isothermal DSC studies conducted at 130, 140, 150, and 160 °C provided additional insight into the time-dependent heat evolution behavior of the material, yielding a comparatively lower activation energy of 99.57 kJ mol^{-1}. The kinetic parameters derived from DSC data were further used to estimate the Time to Maximum Rate under adiabatic conditions (TMRad), an important parameter for thermal hazard assessment. The calculated safety parameters indicated TD8 = 74.60 °C and TD24 = 62.82 °C, suggesting that prolonged exposure of the material above these temperatures could lead to accelerated decomposition. The results provide important thermal safety data for Tenofovir Disoproxil Fumarate and contribute to the establishment of safe storage and processing conditions in pharmaceutical manufacturing environments.

Keywords

Differential Scanning Calorimetry (DSC); Thermal Hazard Assessment; Tenofovir Disoproxil Fumarate; Time to Maximum

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INTRODUCTION

Thermal stability evaluation is an essential aspect in the development, processing, storage, and transportation of pharmaceutical compounds. Active pharmaceutical ingredients (APIs) may undergo exothermic decomposition when exposed to elevated temperatures, which can potentially lead to self-heating, thermal runaway, and safety hazards during manufacturing or storage operations [1,2]. Therefore, understanding the thermal behavior and decomposition kinetics of pharmaceutical substances is critical for ensuring safe process design, regulatory compliance, and risk mitigation in the pharmaceutical industry.

Among the available thermal analysis techniques, Differential Scanning Calorimetry (DSC) is widely used as a rapid and reliable method for assessing the thermal stability and decomposition characteristics of chemical compounds. DSC enables the determination of important thermal parameters such as melting temperature, onset temperature of decomposition, heat flow behavior, and enthalpy changes associated with thermal events [3-5]. In addition, DSC data obtained at multiple heating rates can be utilized to estimate kinetic parameters such as activation energy using Arrhenius-based analysis. These parameters provide valuable insights into the reaction mechanism and thermal sensitivity of materials.

Dynamic DSC experiments are commonly employed to investigate the temperature-dependent behavior of a material under controlled heating conditions, whereas isothermal DSC measurements allow the evaluation of heat evolution as a function of time at a constant temperature [6,7]. The combination of dynamic and isothermal analysis provides a more comprehensive understanding of decomposition kinetics and heat generation behavior [8]. Such information is particularly important in predicting the Time to Maximum Rate under adiabatic conditions (TMRad), a key parameter used in thermal hazard assessment.

The TMRad value represents the time required for a system to reach its maximum self-heating rate and is often used to determine safe storage and operating temperatures for thermally sensitive materials [9,10].

Tenofovir Disoproxil Fumarate (TDF) is a widely used antiviral drug for the treatment of human immunodeficiency virus (HIV) and chronic hepatitis B infections. During pharmaceutical manufacturing and formulation processes, the compound is typically handled in solid form and may be subjected to various thermal environments [11,12]. Although the pharmacological properties of TDF are well established, detailed thermal hazard evaluation is necessary to ensure safe handling, storage, and large-scale processing of the material. Understanding its thermal decomposition behavior and kinetic characteristics is therefore essential for establishing safe operational limits in pharmaceutical manufacturing.

In this study, the thermal decomposition behavior of Tenofovir Disoproxil Fumarate was systematically investigated using dynamic and isothermal Differential Scanning Calorimetry (DSC). Dynamic DSC experiments were performed at different heating rates to analyze thermal transitions and determine kinetic parameters using Arrhenius analysis. Isothermal DSC measurements were conducted at selected temperatures to evaluate time-dependent heat evolution during decomposition. The kinetic data obtained from these experiments were further used to estimate the Time to Maximum Rate (TMRad) and assess the thermal hazard potential of the compound. The results provide important information for evaluating the thermal stability of TDF and contribute to the development of safer storage and processing conditions in pharmaceutical applications.

2 Materials and Methods

2.1 Materials

Tenofovir Disoproxil Fumarate (TDF) was obtained in solid form with pharmaceutical-grade purity and used as received without further purification. The sample was stored in airtight containers under controlled laboratory conditions to prevent moisture uptake prior to analysis. High-purity nitrogen gas was used as the purge atmosphere for DSC experiments. Standard aluminum DSC pans and lids were employed for thermal measurements.

2.2 Differential Scanning Calorimetry (DSC)

Thermal analysis was performed using a calibrated Differential Scanning Calorimeter operating under a nitrogen atmosphere to prevent oxidative interference. Approximately 3–5 mg of TDF was accurately weighed and sealed in aluminum pans for each experiment [13].

2.3 Dynamic DSC Analysis

Dynamic experiments were conducted at multiple linear heating rates of 1, 3, 5, 7, and 9°C min^{-1} over an appropriate temperature range to capture the full decomposition profile. The onset temperature, peak temperature, and heat flow were recorded for each heating rate. The heat release rate (q) was calculated from the exothermic peak, and kinetic parameters were evaluated using the Arrhenius linearization approach. A plot of ln(q) versus 1/T was constructed to determine the activation energy from the slope of the linear fit [14].

2.4 Isothermal DSC Analysis

Isothermal experiments were performed at selected temperatures (130, 140, 150, and 160˚C) to evaluate decomposition behavior under constant-temperature conditions. The heat flow as a function of time was monitored, and peak heat generation rates were recorded. Activation energy was determined using iso-conversional analysis based on the Arrhenius relationship [15].

2.5 Estimation of Time to Maximum Rate (TMRad)

Time to Maximum Rate under adiabatic conditions (TMRad) was estimated using kinetic parameters obtained from DSC data. A zero-order approximation was assumed for conservative hazard prediction. The Frank-Kamenetskii method was applied to calculate TMRad at various temperatures. Specific heat capacity values were incorporated into the calculations to estimate self-heating behavior and safe storage limits [9].

2.6 Data Analysis

All experiments were conducted in duplicate to ensure reproducibility. Linear regression analysis was used to determine activation energy and correlation coefficients (R^2). Comparative evaluation between dynamic and isothermal DSC modes was performed to assess the reliability and conservativeness of hazard predictions.

3 Results and Discussions

3.1 DSC analysis in Dynamic mode:

Dynamic Differential Scanning Calorimetry (DSC) was performed at heating rates of 1, 3, 5, 7, and 9 °C min^{-1} to investigate the thermal decomposition behavior of Tenofovir Disoproxil Fumarate (TDF). As shown in Figure 1 - 5, the DSC thermograms reveal similar thermal features across all heating rates, consisting of an initial endothermic melting event followed by two exothermic decomposition stages. However, the position and intensity of these peaks vary with heating rate due to kinetic effects.

The first thermal event observed in all thermograms is a sharp endothermic peak occurring between approximately 108–116°C, corresponding to the melting of crystalline TDF. At 1°C min^{-1}, the melting

peak appears at 111.92°C, while at higher heating rates (3–9°C min^{-1}) the peak slightly shifts to 112–116°C. This shift toward higher temperatures with increasing heating rate is a common kinetic phenomenon caused by thermal lag and delayed heat transfer, indicating that the melting process is sensitive to the heating conditions [16].

Following the melting transition, a broad exothermic peak representing the primary decomposition stage is observed. The onset temperature of this decomposition shifts significantly with heating rate. At 1°C min^{-1}, the exothermic decomposition begins near 138°C with a peak around 188°C. As the heating rate increases, the onset temperature moves to higher values, reaching approximately 165°C at 3°C min^{-1}, ~182°C at 5°C min^{-1}, ~129–219°C region at 7°C min^{-1}, and approximately 191–224°C at 9°C min^{-1}. The increasing peak temperature with heating rate confirms that the decomposition process is kinetically controlled, meaning that the reaction rate strongly depends on temperature [17].

The enthalpy released during the primary exothermic event is substantial, indicating significant energy release during molecular breakdown. The exothermic peak width also becomes broader at higher heating rates, suggesting that the decomposition proceeds through multiple overlapping reaction steps, possibly involving the cleavage of ester bonds and degradation of intermediate products.

A secondary exothermic decomposition stage appears at higher temperatures (approximately 310–350°C) for heating rates of 5, 7, and 9°C min^{-1}. This peak corresponds to further degradation of intermediate residues formed during the primary decomposition stage. The presence of multiple exothermic stages suggests that the thermal degradation of TDF occurs through a multi-step reaction mechanism rather than a single-step process [18,19].

The DSC analysis demonstrates that increasing the heating rate results in systematic shifts of onset, peak, and endset temperatures toward higher values, while maintaining similar decomposition patterns. This behavior confirms the kinetic nature of the decomposition process and supports the use of multiple heating rates for reliable kinetic analysis as shown in Figure 6. The summary of the analysis is depicted in Table 1. The data obtained from these experiments provide essential parameters for calculating activation energy and predicting Time to Maximum Rate (TMRad), a thermal hazard parameteras in Table 2.

From a safety perspective, the presence of strong exothermic decomposition following melting indicates that thermal runaway may occur if the material is exposed to elevated temperatures under confined conditions. Therefore, understanding the heating rate dependence of decomposition behavior is crucial for safe storage, transportation, and large-scale pharmaceutical processing of Tenofovir Disoproxil Fumarate.

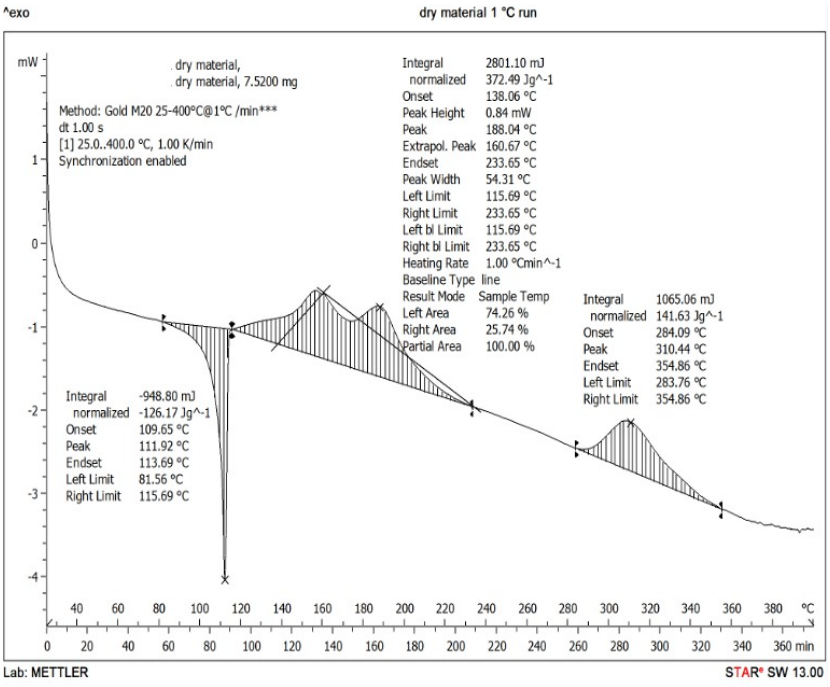


Fig. 1DSC graph obtained with the heating rate of 1°C/min

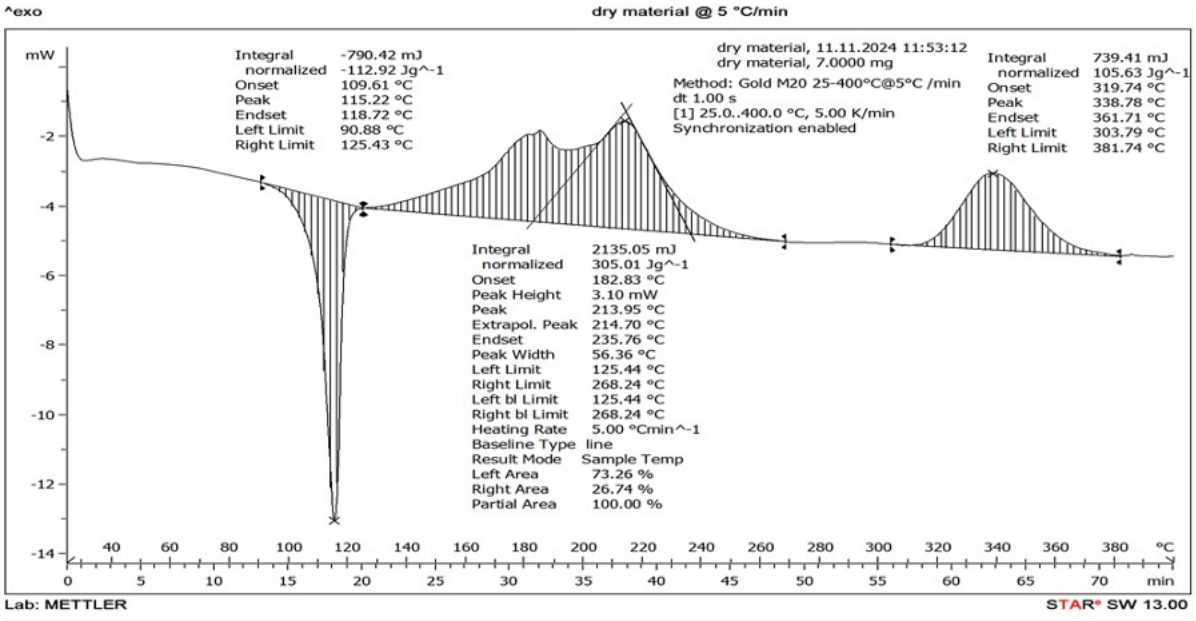


Fig. 2DSC graph obtained with the heating rate of 3°C/min

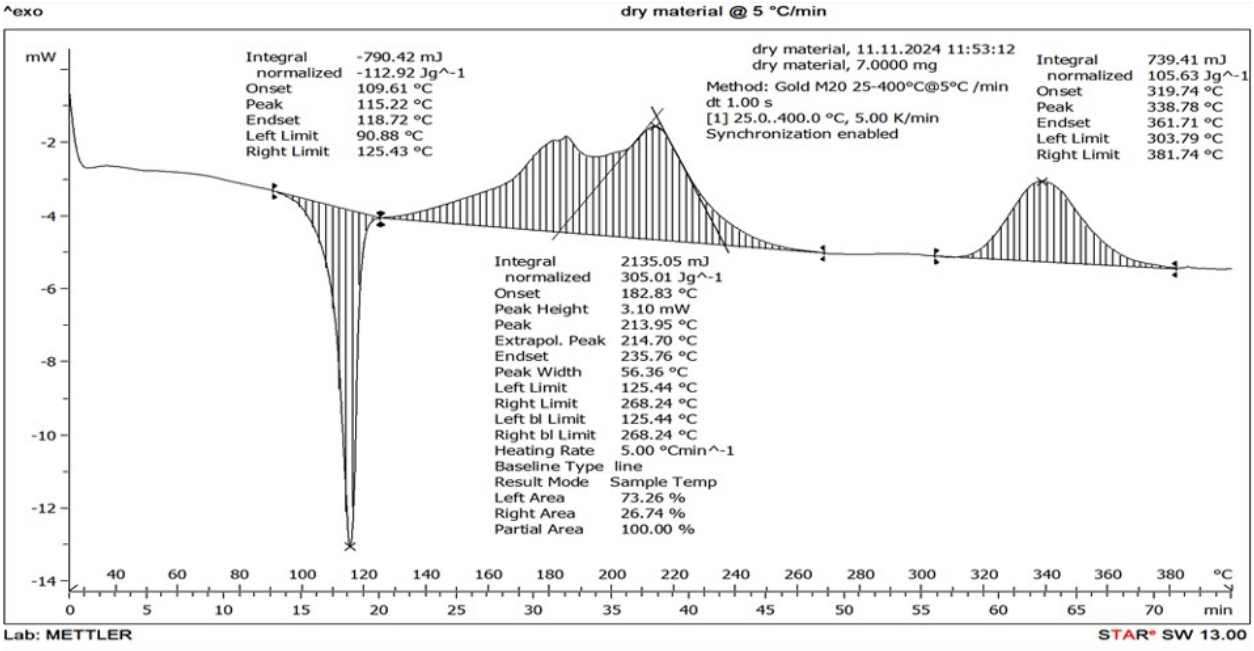


Fig. 3DSC graph obtained with the heating rate of 5°C/min

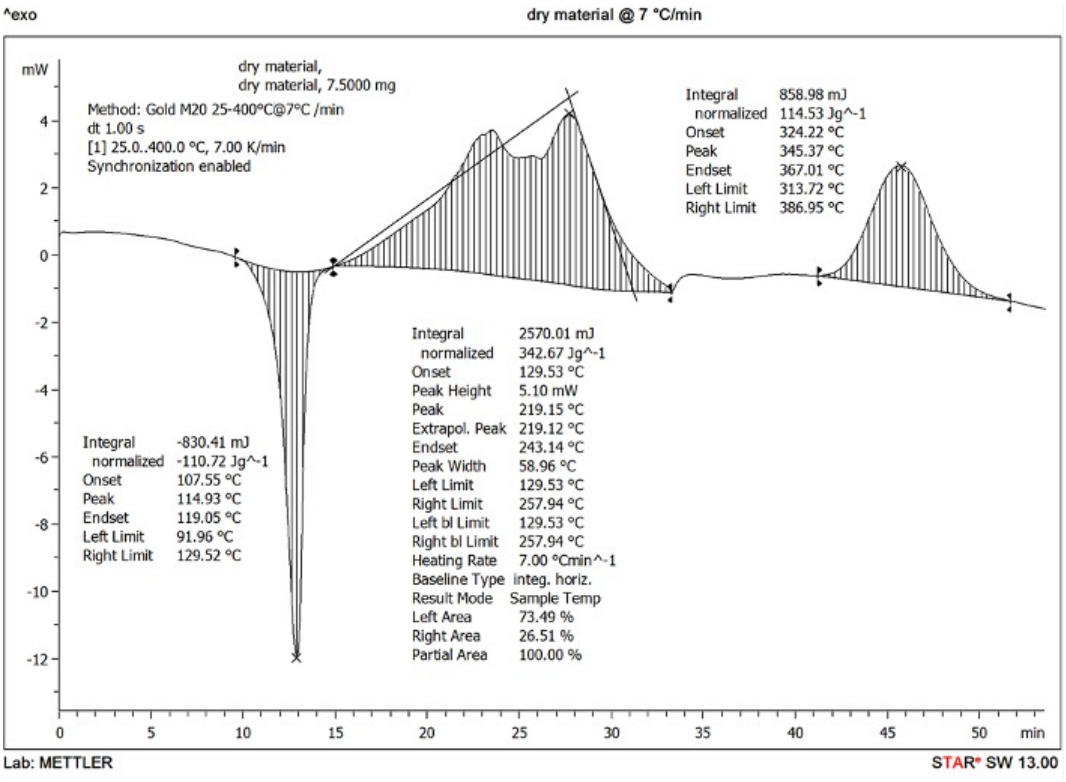


Fig. 4DSC graph obtained with the heating rate of 7°C/min

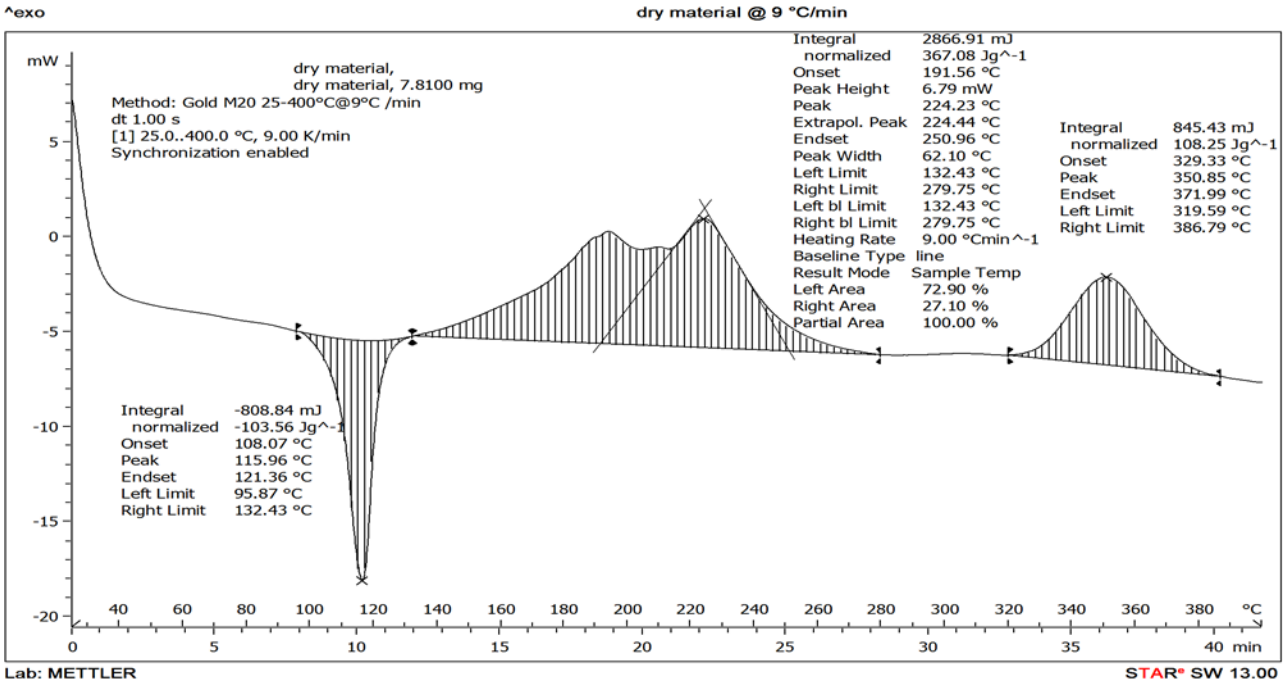


Fig. 5 DSC graph obtained with the heating rate of 9°C/min

Table 1 Summary of the DSC dynamic mode analysis

S.No	Onset temperature (°C)	Onset temperature (°C)	Temperature (K)	1/T	q (W/kg)	Lnq
1	Heating rate @1 °C/min	115.7	388.8500	0.002572	111.7021	4.72
2	Heating rate @3 °C/min	119.5	392.6500	0.002547	244.6043	5.50
3	Heating rate @5 °C/min	125.4	398.5500	0.002509	442.8571	6.09
4	Heating rate @7 °C/min	129.5	402.6500	0.002484	680	6.52
5	Heating rate @9 °C/min	132.4	405.5500	0.002466	869.3982	6.77

As per the analysis results the onset of temperature was shifted in slighter high condition i.e higher in temperature side.

- The slope calculated is -18684.98
- The activation energy is: 155.34 kJ/mol.
- Specific heat capacity.: 2 J/g°C

Table 2 CalculatedTMRad at different temperature in dynamic mode

T °C	1/T	W/kg	TMRad (h)
30.00	0.0033	0.0001	19390.94
40.00	0.0032	0.0010	2890.66
50.00	0.0031	0.0064	485.75
60.00	0.0030	0.0362	91.02
65.00	0.0030	0.0830	40.92
68.42	*0.0029*	*0.1444*	*24.01*
70.00	0.0029	0.1857	18.84
75.69	*0.0029*	*0.4514*	*8.01*
80.00	0.0028	0.8678	4.27
90.00	0.0028	3.7256	1.05
100.00	0.0027	14.7920	0.28

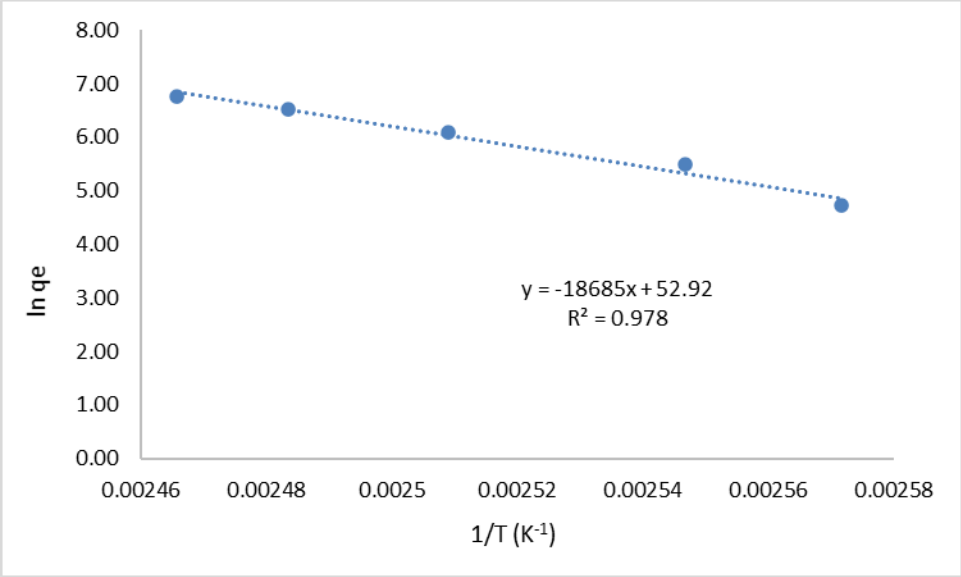


Fig. 6 Arrhenius plot of ln qe versus 1/T

3.2 Time to Maximum Rate (TMRad) studies of Dynamic mode

The TMRad curve presented illustrates the thermal stability profile of the substance or reaction system studied as shown in Figure 7. The curve plots temperature (°C) as a function of time (hrs), showing how the system behaves under adiabatic conditions.

Two critical parameters are identified from the curve:

- TD8 = 75.69°C: This is the temperature at which the time to maximum rate is 8 hours. It indicates that if the system reaches this temperature, it will take 8 hours to reach the maximum reaction rate under adiabatic conditions.
- TD24 = 68.42°C: This is the temperature at which the time to maximum rate is 24 hours. It represents a lower temperature threshold where the system takes 24 hours to reach the maximum rate.

These values are essential for process safety assessments. The TD24 value, in particular, is often used as a reference for defining safe handling and storage temperatures. A lower TD24 indicates higher thermal sensitivity. In this case, the TD24 of 68.42°C suggests that the material should be kept below this temperature to ensure a sufficient safety margin during processing or storage [20,21].

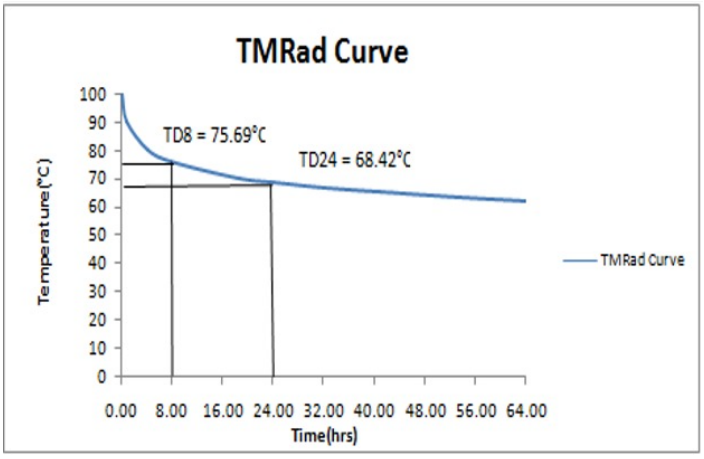


Fig. 7 Obtained TMRad Curve in dynamic mode

3.3DSC analysis in Isothermal mode:

Isothermal Differential Scanning Calorimetry (DSC) experiments were carried out at 130, 140, 150, and 160 °C to investigate the time-dependent thermal decomposition behavior of Tenofovir Disoproxil Fumarate (TDF) under constant temperature conditions as shown in Figure 8 - 11. Unlike dynamic DSC, isothermal measurements allow direct monitoring of heat evolution as a function of time, which provides more reliable information about reaction kinetics and the onset of self-heating behavior.

At 130 °C, the DSC curve shows a slow and gradual exothermic heat release after the sample reaches the set temperature. The peak heat flow is relatively small (≈0.37 mW), and the total heat released is 281.16 J g^{-1}. The heat flow decays slowly over the duration of the experiment, indicating that decomposition occurs at a very slow rate at this temperature. This suggests that TDF exhibits moderate thermal stability near 130 °C, with the reaction proceeding gradually without rapid heat accumulation [22].

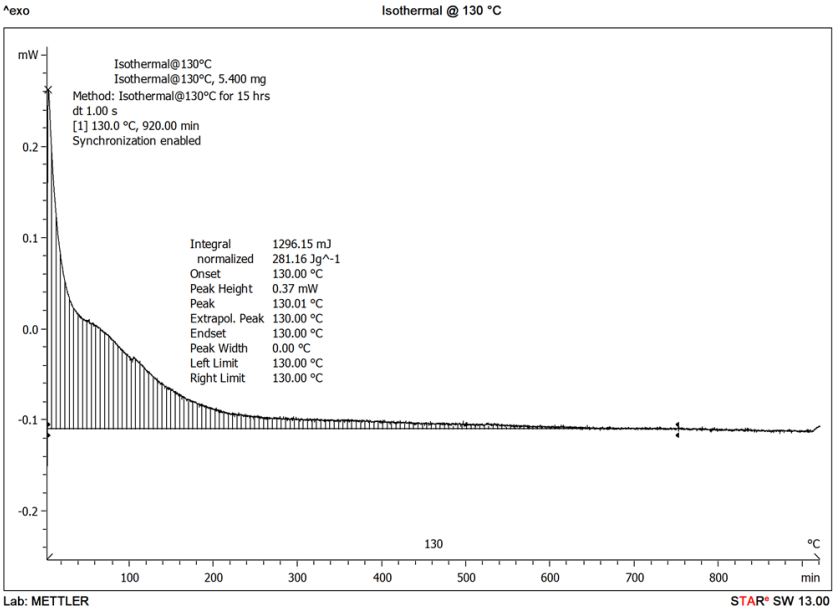
When the temperature is increased to 140 °C, the exothermic behavior becomes more pronounced. The maximum heat flow increases to ≈0.79 mW, and the total heat release rises slightly to 285.09 J g^{-1}. The initial heat evolution occurs more rapidly than at 130 °C, indicating that the decomposition reaction rate increases significantly with temperature. Although the reaction still proceeds relatively slowly, the higher heat flow demonstrates enhanced molecular degradation at this temperature [23].

At 150 °C, the decomposition reaction accelerates further. The peak heat flow increases to ≈0.84 mW, while the integrated heat release increases to 336.79 J g^{-1}. The faster decay of the heat flow curve suggests that a larger portion of the decomposition reaction occurs in the early stages of the experiment, followed by gradual completion over time. This behavior indicates that thermal degradation becomes increasingly significant above 150 °C [24,25].

At the highest investigated temperature, 160 °C, the DSC thermogram shows the most rapid heat evolution. The peak heat flow increases to ≈0.98 mW, and the total heat release reaches 371.97 J g^{-1}. The heat flow decreases rapidly after the initial stage, indicating that the decomposition reaction proceeds much faster at this temperature. The increased heat generation demonstrates that the system approaches more vigorous exothermic decomposition conditions [26].

The isothermal DSC results demonstrate a strong temperature dependence of the decomposition kinetics of TDF. As the temperature increases from 130 to 160 °C, both the heat generation rate and the total heat released increase, while the reaction time required for decomposition decreases. This behavior confirms that the degradation process follows thermally activated kinetics, consistent with Arrhenius-type behavior as shown in Figure 12.The summary of the analysis is depicted in Table 3. The data obtained from these experiments provide essential parameters for calculating activation energy and predicting Time to Maximum Rate (TMRad), a thermal hazard parameter as in Table 4.

From a thermal safety perspective, the results indicate that prolonged exposure of TDF above 140–150 °C significantly accelerates decomposition, which could lead to heat accumulation in large-scale systems. Therefore, these isothermal data provide critical information for kinetic modeling, prediction of Time to Maximum Rate (TMRad), and



determination of safe operating and storage temperatures for Tenofovir Disoproxil Fumarate in pharmaceutical processing.

Fig. 8 DSC graph obtained at 130°C

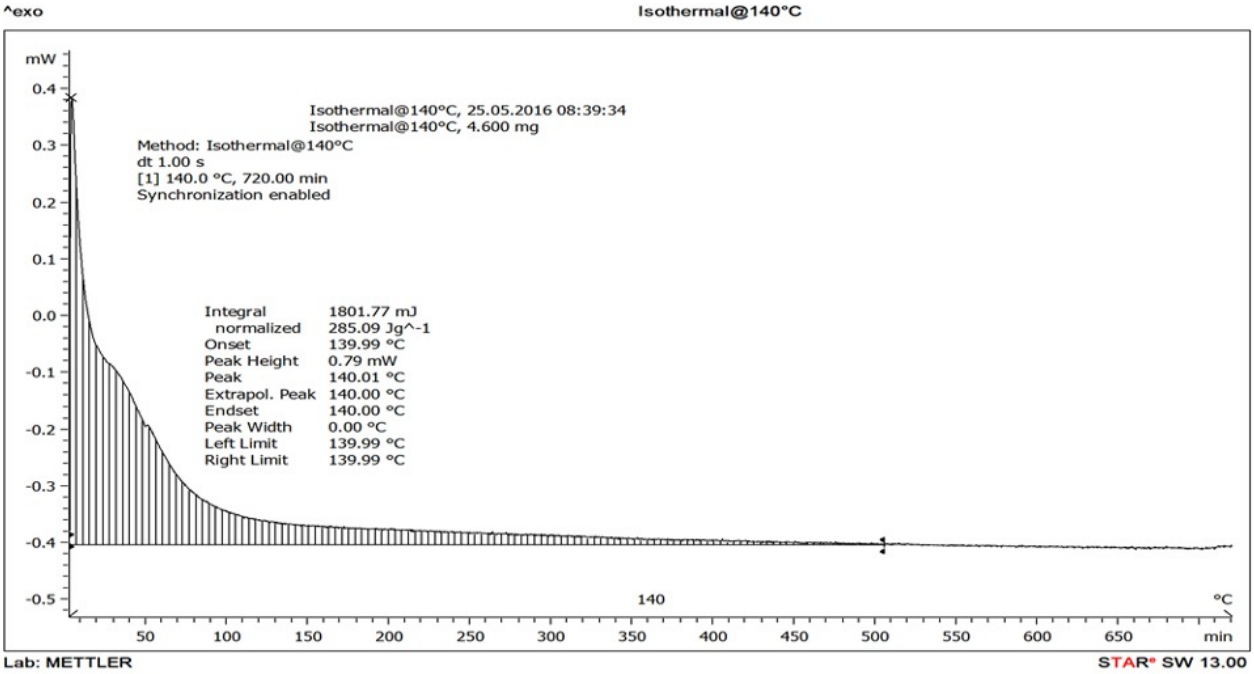


Fig. 9 DSC graph obtained at 140°C

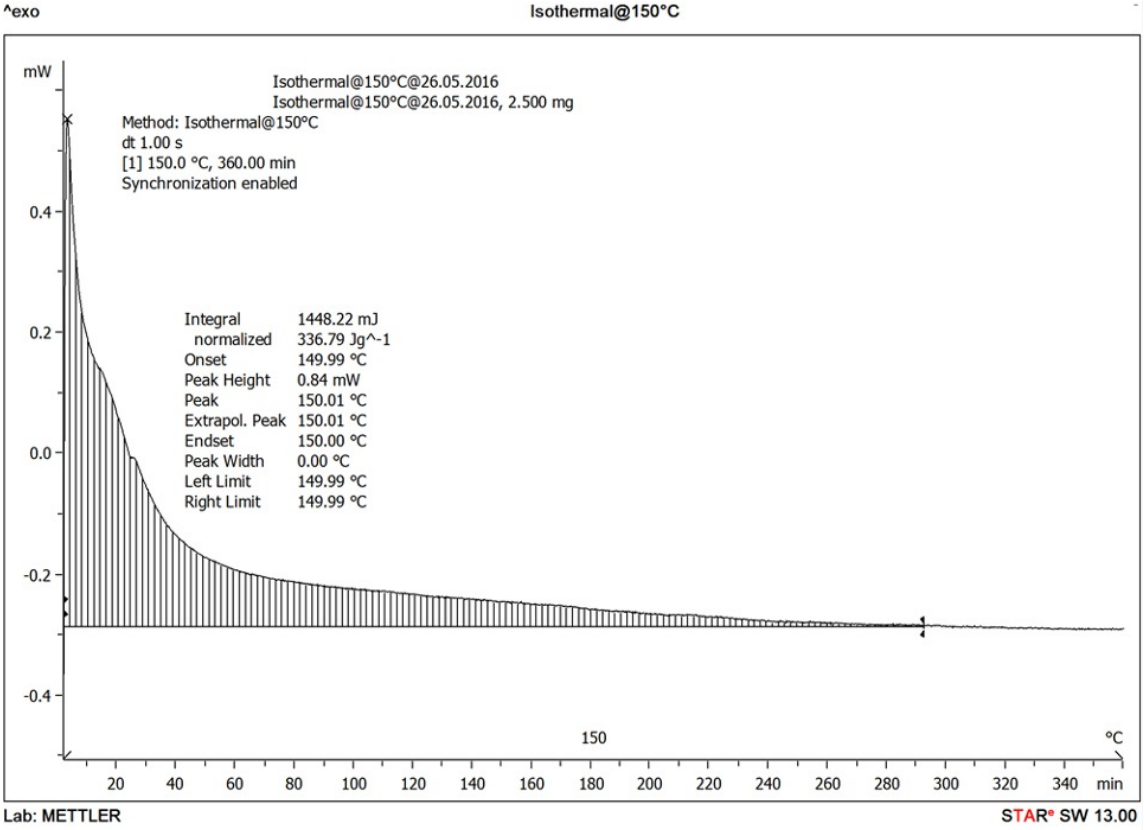


Fig. 10 DSC graph obtained at 150°C

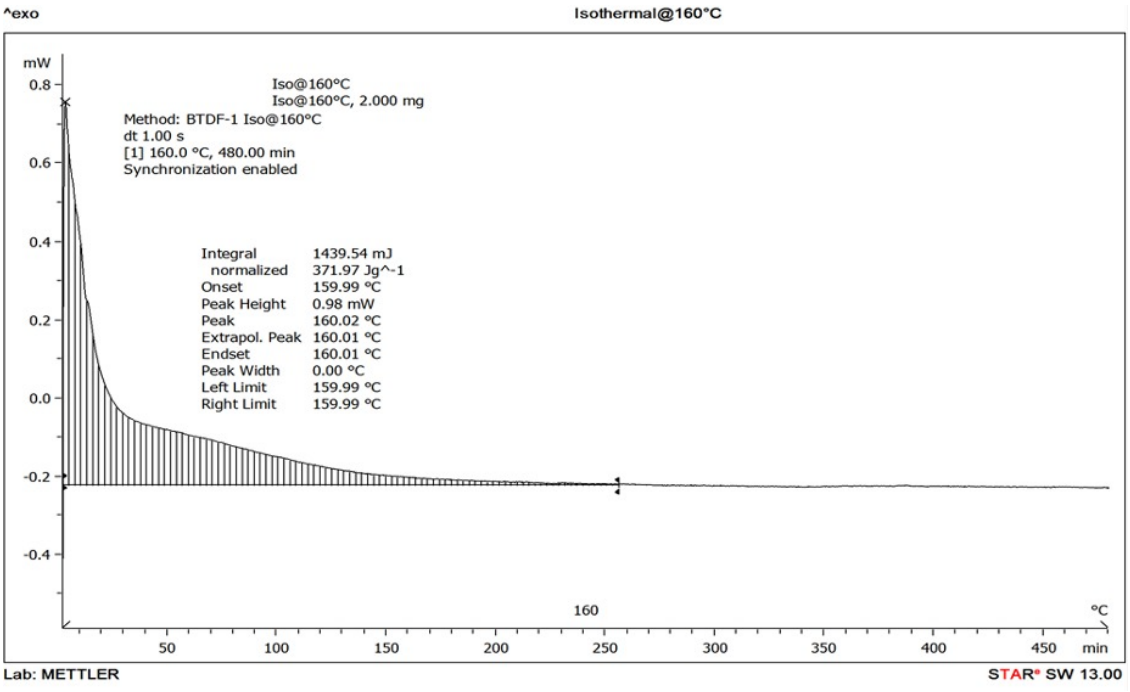


Fig. 11 DSC graph obtained at 160°C

Table 3 Summary of the DSC Isothermal mode analysis

S.No	Onset temperature (°C)	Onset temperature (°C)	Temperature (K)	1/T	q (W/kg)	Lnq
1	Isothermal at 130 °C	130	403.1500	0.00248	68.51852	4.23
2	Isothermal at 140 °C	140	413.1500	0.00242	171.7391	5.15
3	Isothermal at 150 °C	150	423.1500	0.002363	336	5.82
4	Isothermal at 160 °C	160	433.1500	0.002309	490	6.19

- The slope calculated is -1159.39
- The activation energy is: 99.57 kJ/mol.
- Specific heat capacity.: 2 J/g°C

Table 4 Calculated TMRad at different temperature in Isothermal mode

T°C	1/T	W/kg	TMRad (h)
30.00	0.0033	0.0055	801.36
40.00	0.0032	0.0186	254.12
50.00	0.0031	0.0580	86.69
60.00	0.0030	0.1692	31.61
62.82	0.0030	0.2262	24.05
68.42	0.0029	0.3968	14.17
70.00	0.0029	0.4635	12.24
74.60	0.0029	0.7226	8.06
80.00	0.0028	1.1991	5.01
82.25	0.0028	1.4742	4.13
90.30	0.0028	3.0222	2.11
93.17	0.0027	3.8741	1.67
100.00	0.0027	6.8888	0.97

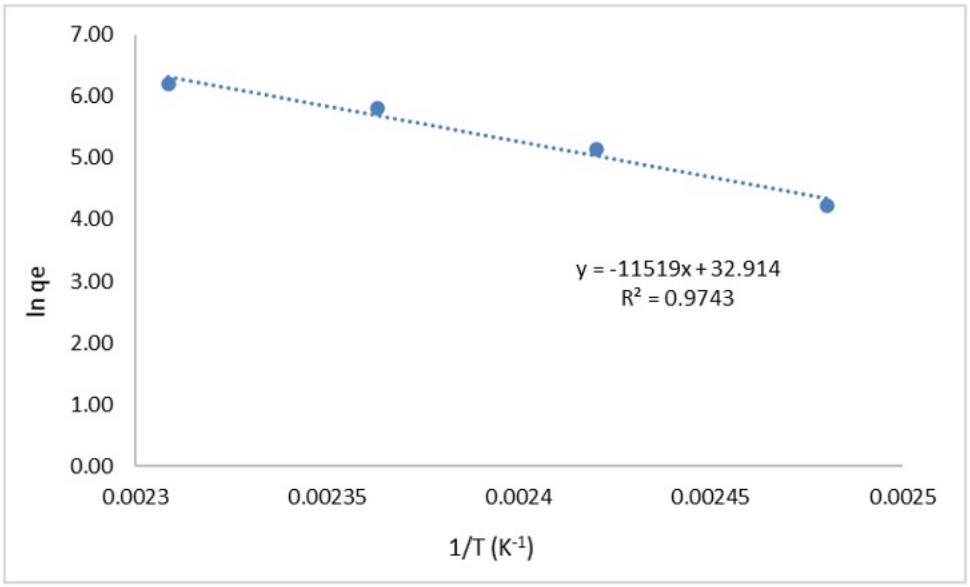


Fig. 12 Arrhenius plot of ln qe versus 1/T

3.4Time to Maximum Rate (TMRad) studies of dynamic mode

The Time to Maximum Rate under adiabatic conditions (TMRad) curve shown in Figure 13 illustrates the predicted thermal stability behavior of Tenofovir Disoproxil Fumarate based on kinetic parameters obtained from Differential Scanning Calorimetry (DSC) analysis. The curve represents the relationship between temperature (°C) and time to maximum reaction rate (hours) under simulated adiabatic conditions. This relationship provides important information regarding the self-heating tendency and potential thermal hazard of the material.

From the TMRad curve, two key safety parameters can be determined:

- TD8 = 74.60°C: This temperature corresponds to the condition at which the time required for the system to reach the maximum self-heating rate is 8 hours. If the material reaches this temperature, the decomposition reaction is expected to accelerate and reach its maximum rate within this time period.
- TD24 = 62.82°C: This value represents the temperature at which the time to maximum reaction rate is 24 hours. The TD24 value is commonly used as a reference temperature for safe storage and handling, as it provides a conservative estimate of the temperature below which the material can remain thermally stable for an extended period.

The decreasing trend observed in the TMRad curve indicates that as the temperature increases, the time required to reach the maximum reaction rate decreases significantly, reflecting the strong temperature dependence of the decomposition kinetics of Tenofovir Disoproxil Fumarate.

From a safety standpoint, the TD24 value of 62.82°C suggests that the material should be stored and processed at temperatures well below this threshold to maintain an adequate safety margin and minimize the risk of thermal runaway during pharmaceutical manufacturing and storage operations [20,21].

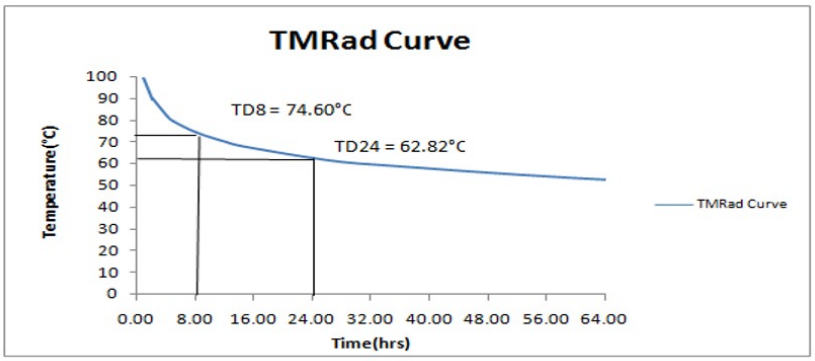


Fig. 13 Obtained TMRad Curve in isothermal mode

4. Compative study of DSC Dynamic and Isothermal mode

A comparative evaluation of the Time to Maximum Rate under adiabatic conditions (TMRad) obtained from dynamic and isothermal DSC analyses is presented in Table 5. The comparison focuses on two commonly used safety criteria, namely TD8 (temperature corresponding to a TMRad of 8 hours) and TD24 (temperature corresponding to a TMRad of 24 hours). These parameters are widely used in thermal hazard assessment to establish safe storage and operating limits for thermally sensitive materials.

From the dynamic DSC analysis, the calculated temperatures corresponding to TMRad values of 8 h and 24 h were 75.69°C and 68.42°C, respectively. In contrast, the isothermal DSC analysis yielded slightly lower temperatures of 74.60°C for TD8 and 62.82°C for TD24. The lower TD24 value obtained from the isothermal analysis indicates a more conservative estimation of the thermal stability limit of the material[17,27].
The small difference observed between the two modes suggests that both dynamic and isothermal DSC methods provide consistent predictions of the thermal hazard behavior of Tenofovir Disoproxil Fumarate. However, the isothermal DSC results tend to predict slightly lower safety threshold temperatures, which may be attributed to the direct monitoring of heat evolution under constant temperature conditions. This allows a more realistic representation of decomposition kinetics compared to dynamic heating conditions.

Table 5. Comparison of TMRad values obtained from dynamic and isothermal DSC analyses

S.No	Time at which calculated (h)	TMRad Dynamic mode	TMRad isothermal mode
1	8	75.69	74.60
2	24	68.42	62.82

Conclusions:
The thermal stability and decomposition behavior of Tenofovir Disoproxil Fumarate were investigated using dynamic and isothermal Differential Scanning Calorimetry (DSC). Dynamic DSC analysis at different heating rates revealed a melting transition followed by exothermic decomposition, with an activation energy of 155.34 kJ mol^{-1} obtained from Arrhenius analysis. Isothermal DSC experiments conducted at 130–160 °C provided additional insight into the time-dependent heat evolution behavior and yielded a lower activation energy of 99.57 kJ mol^{-1}, indicating a more conservative estimation of thermal hazard.The kinetic parameters derived from DSC data were used to estimate the Time to Maximum Rate under adiabatic conditions (TMRad). The calculated safety parameters TD8 (74.60 °C) and TD24 (62.82 °C) indicate that exposure of the material above these temperatures may accelerate decomposition and increase the risk of self-heating. The comparative analysis of dynamic and isothermal DSC modes showed good agreement in predicting the thermal hazard behavior of the compound. This study provides important information on the thermal decomposition characteristics and hazard potential of Tenofovir Disoproxil Fumarate, which can be useful for establishing safe storage, handling, and processing conditions in pharmaceutical manufacturing.

Statement & Declarations

Declaration: The authors declare that this work was not carried out by anyone so far.

Competing Interest: Authors have no relevant financial or non-financial interest to disclose.

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