

Thermal decomposition kinetics of 5-fluorouracil from thermogravimetric analysis

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Abstract—The thermal decomposition kinetics of 5-fluorouracil was studied by thermogravimetric analysis methodology. The decomposition activation energy was calculated by using Ozawa method by means of TGA in nitrogen atmosphere. Moreover, the decomposition mechanism and pre-factor were obtained by Coats-Redfern and Achar methods, respectively. It is found that the decomposition activation energy of fluorouracil is 105 kJ·mol⁻¹. The decomposition mechanisms obtained by Coats-Redfern and Achar methods are $G(\alpha)=[-\ln(1-\alpha)]^{2/3}$ and $f(\alpha)=1.5(1-\alpha)[- \ln(1-\alpha)]^{1/3}$ respectively, $\ln A$ is 21.40 min⁻¹.

Key words: 5-Fluorouracil, Thermal Degradation Kinetics, Decomposition Activation Energy, Solid-state Function

INTRODUCTION

Reports of attempts to investigate the physicochemical properties of 5-fluorouracil and hence improve its topical, oral or rectal properties are quite extensive in the prodrug literature because of increasing the breadth of its indicated uses, especially in the anti-cancer and antitumor fields [1]. Generally, for highly polar molecules such as 5-fluorouracil, how to exhibit the effective action on the target sites in vitro has been reported by using various methods, such as thermogravimetric analysis methodology [2-6]. Storage stability of compounds of medical interest is also important [7]. To establish relative stability and physicochemical properties of 5-fluorouracil, the thermal process of 5-fluorouracil was investigated by means of thermogravimetric analysis methodology. Activation energy and other thermodynamic parameters were deduced according to thermogravimetric analysis methodology.

EXPERIMENTAL SECTION

The 5-fluorouracil was purchased from Jinan Medicine Company, at least 99% pure. Thermal gravimetric analysis was carried out in nitrogen flow in Thermal Analysis Co., Model 2950 system. Samples of 6 mg placed in standard aluminum cups were used for test in a TA SDTQ600 thermogravimetric analyzer. The Samples were heated from 200 °C to 400 °C at the heating rates of 5, 10, 20 and 30 °C min⁻¹.

RESULTS AND DISCUSSION

1. The Decomposition Activation Energy

Kinetic information could be extracted from dynamic experiments by means of various methods. Ozawa [8] method was a model-free method which assumed that the conversion function did not change with the alteration of all the heating rates. It involved measuring of the temperatures corresponding to fixed values of α from experiments at different heating rates β . We used the model-free method

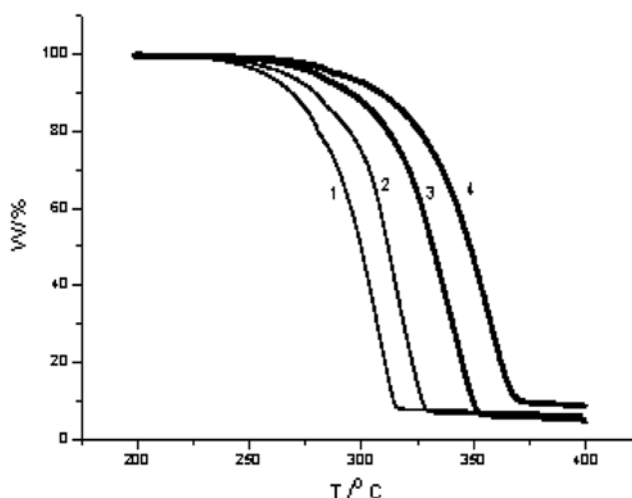


Fig. 1. TGA thermograms of fluorouracil at different heating rates (1. $\beta=5^{\circ}\text{C}\cdot\text{min}^{-1}$, 2. $\beta=10^{\circ}\text{C}\cdot\text{min}^{-1}$, 3. $\beta=20^{\circ}\text{C}\cdot\text{min}^{-1}$, 4. $\beta=30^{\circ}\text{C}\cdot\text{min}^{-1}$).

based on Eq. (1) to perform the kinetic analysis:

$$\log F(\alpha) = \log A \frac{E}{R} - \log \beta - 2.315 - 0.4567 \frac{E}{RT} \quad (1)$$

Plotting $\log \beta$ against $1/T$ should give straight lines and their slopes were proportional to the activation energies ($-E/R$). Thermograms of 5-fluorouracil at heating rates of 5, 10, 20 and 30 °C·min⁻¹ under nitrogen are shown in Fig. 1. The TGA thermograms suggest that the fluorouracil undergoes a rapid decomposition within a narrow temperature range and the total loss mass for 5-fluorouracil at different heating rates is up to 90%.

The heating rates at different conversions obtained from the TGA thermograms versus $1/T$ curves are plotted in Fig. 2; the correlation yielding straight lines exceeds 0.99. More often, the apparent activation energy of the decomposition process usually varies with the extent of conversion and this phenomenon is a signal of complex reaction in the thermal process. However, the activation energies for varying conversion extents all approach to 105 kJ mol⁻¹ under

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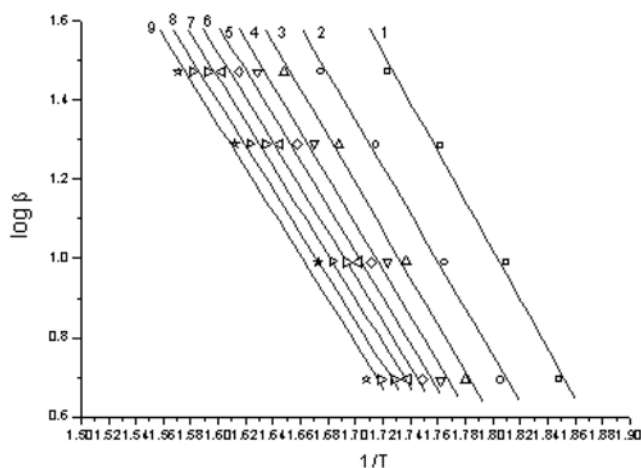


Fig. 2. $\log \beta$ as function of $1/T$ at different conversions (1. $\alpha=0.1$, 2. $\alpha=0.2$, 3. $\alpha=0.3$, 4. $\alpha=0.4$, 5. $\alpha=0.5$, 6. $\alpha=0.6$, 7. $\alpha=0.7$, 8. $\alpha=0.8$, 9. $\alpha=0.9$).

nitrogen atmosphere, which suggests that the decomposition of fluorouracil undergoes one stage mechanism.

2. Determination of Kinetic Parameters

As indicated previously, the decomposition of 5-fluorouracil likely proceeds as a one stage mechanism. In order to determine kinetics parameters in a solid-state decomposition reaction, usually data was obtained at various methods. In our present study of kinetics of solid-state reaction leading to the decomposition of the material, two equations, viz., Coats-Redfern and Achar, were used for calculating the mechanism function and pre-factor.

The Coats-Redfern [9] method uses an asymptotic approximation for the resolution of kinetic equation. According to Doyle approximation, the equation could be written as $\ln[(g(\alpha)/T^2)] = \ln(AR/bE) - (E/RT)$. According to the different degradation processes, with the theoretical function $g(\alpha)$ being listed in Table 1, E and A could be obtained from the plots of $\ln[G(\alpha)/T^2]$ versus $1/T$, as well as the valid reaction mechanism. Achar [10] proposed the use of the logarithm of the conversion rate as a function of the reciprocal temperature, that was $\ln[(d\alpha/dT)/f(\alpha)] = \ln(A/\beta) - (E/RT)$. It was obvious if the function $f(\alpha)$ was constant for a particular value of α . Plotting $\ln[d\alpha/dT/f(\alpha)]$ against $1/T$ should give straight lines with their slopes proportional to the activation energies $(-E/R)$.

To investigate the solid-state process of 5-fluorouracil, Coats-Redfern and Achar methods were chosen as they both involved the mechanisms of solid-state process. According to the function [11] listed in Table 1, different mechanism functions were chosen to calculate the activation energies using Coats-Redfern and Achar methods, the results of which are in comparison to the activation energy

Table 1. $g(\alpha)$ for the most frequently used mechanisms of solid-state processes

Mechanism function	Solid-state process
$[-\ln(1-\alpha)]^n$ ($n=1/4, 1/3, 2/5, 1/2, 2/3, 3/4, 1, 3/2, 2, 3, 4$)	Nucleation and growth
α	Phase boundary controlled reaction
$2[1-\ln(1-\alpha)^{1/2}]$	Phase boundary controlled reaction
α^2	One-dimensional diffusion
$(1-\alpha)\ln(1-\alpha)+\alpha$	Two-dimensional diffusion

obtained by Ozawa method. The activation energies corresponding to the mechanism function $G(\alpha)=[-\ln(1-\alpha)]^{2/3}$ and $f(\alpha)=1.5(1-\alpha)[-\ln(1-\alpha)]^{1/3}$ obtained by Coats-Redfern and Achar methods, respectively, are in good agreement with Ozawa methods, and the pre-factor $\ln A$ is 21.40 min^{-1} . The thermal decomposition rate equation of 5-fluorouracil is $(d\alpha/dt)=3.0 \times 10^9(1-\alpha)[-\ln(1-\alpha)]^{1/3}\exp(-E/RT)$.

CONCLUSION

The non-thermal kinetics of 5-fluorouracil was investigated by thermogravimetric analysis under nitrogen atmosphere; it was found that the 5-fluorouracil undergoes one stage mechanism from 200°C to 400°C and the total loss is similar at 90%. The decomposition activation energy of fluorouracil calculated by Ozawa method is 105 kJ mol^{-1} . Furthermore, the thermal process decomposition functions obtained by Coats-Redfern and Achar methods are $G(\alpha)=[-\ln(1-\alpha)]^{2/3}$ and $f(\alpha)=1.5(1-\alpha)[-\ln(1-\alpha)]^{1/3}$ respectively, and the pre-factor $\ln A$ is 21.40 min^{-1} . The correlations yielding straight lines for Ozawa, Coats-Redfern and Achar methods all exceed 0.99.

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