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SHORT COMMUNICATION

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, lnA 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 anticancer 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 ºC to 400 ºC at the heating rates of 5, 10, 20 and 30 ºC 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 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 heating rates of 5, 10, 20 and 30 ºC·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%.

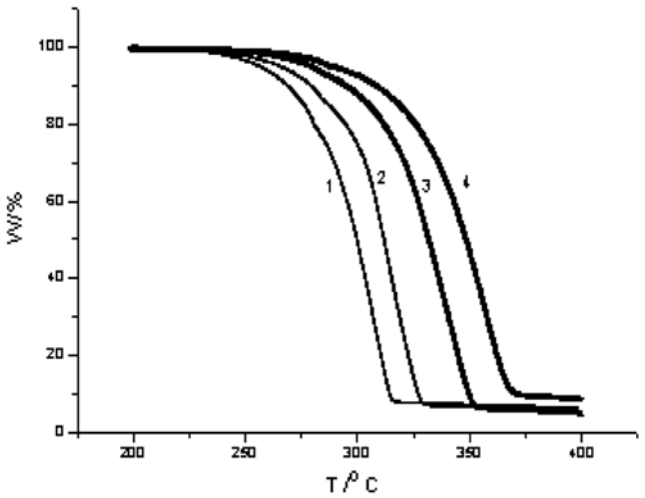

Fig. 1. TGA thermograms of fluorouracil at different heating rates (1. β=5 ºC·min^{-1}, 2. β=10 ºC·min^{-1}, 3. β=20 ºC·min^{-1}, 4. β= 30 ºC·min^{-1}).

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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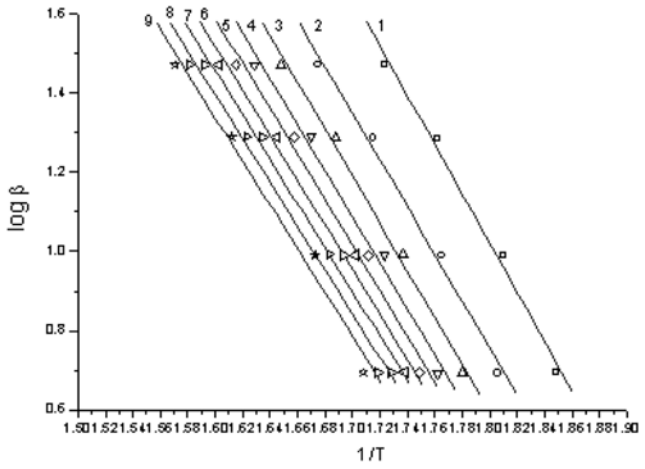

Fig. 2. logβ as function of 1/T at different conversions (1. α=0.1, 2. α=0.2, 3. α=0.3, 4. α=0.4, 5. α=0.5, 6. α=0.6, 7. α=0.7, 8. α=0.8, 9. α=0.9).

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(α) 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 lnA is 21.40 min^{-1}. The thermal decomposition rate equation of 5-fluorouracil is $(d\alpha/dt)=3.0\times10^9(1-\alpha)[-\ln(1-\alpha)]^{1/3}\exp(-E/RT)$.

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 lnA 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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