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EFFECTS OF EXPERIMENTAL CONDITIONS ON THE ESTIMATION OF KINETIC PARAMETERS OF THE THERMAL DECOMPOSITION OF AZT USING FACTORIAL DESIGN

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The influence of experimental conditions on the kinetic parameters of solid-state reactions using thermogravimetry (TG) has been investigated for different materials. The evaluation of these thermal curves is used for the determination of the activation energy, E_a, the pre-exponential factor, A, and the function of the reaction extent, $f(\alpha)$ by the kinetic analysis for TG (Shimadzu software) based on the Ozawa method. Factorial designs are excellent tools for determining the effects of a wide variety of factors on the results of complex processes. Here a 2^4 factorial design was used to investigate the influence of four variables (sample mass, furnace environment, furnace atmosphere and sample container composition) on the estimation of kinetic parameters of the thermal decomposition of a zidovudine (AZT) pharmaceutical formulation. TG curves registered at five different heating rates showed that AZT has five stages of mass loss in the following temperature ranges: 25–130, 195–270, 270–350, 350–400 and 400–590°C. These events are characterized by the release of water molecules, thermal decomposition in three stages, followed by the elimination of carbonaceous materials. The average value obtained for E_a using the TG curves in different experimental conditions was 119 kJ mol^{-1}. The variability study of the influence of different experimental conditions of TG, using the factorial design, indicates with 95% probability that none of the analyzed effects were significant for the AZT sample.

Keywords: *factorial design, kinetics analysis, thermal analysis, zidovudine (AZT)*

Introduction

Research in thermal decomposition of drugs is of great interest in developing new products since it is often necessary to predict degradation rates at marketing temperatures from data collected on accelerated processes studied at elevated temperatures [1, 2]. In pharmaceutical sciences thermal methods of analysis have found important applications, among them the determination of kinetics parameters [3, 4]. For this purpose various types of thermal analysis techniques have been applied to almost all fields, including materials chemistry and more particularly pharmaceutical products [5–10]. Thermogravimetry (TG), in which the change in mass of a sample heated at constant rate is recorded and plotted *vs*. temperature, is an effective method of studying thermal stability and for determining the kinetic parameters of the decomposition of drugs and medicines [11–12].

The fact that the temperature is altered in thermal analysis means that special considerations must be given to thermodynamic and kinetic factors. Thermodynamics deals with the equilibrium condition at any temperature. In kinetics, the emphasis is on the reaction rate. In TG, the substance mass as a function of time and temperature is used to assess the thermal stability and degradation of drugs, which includes the generation of kinetic data such as activation energies [13]. However, there are many methods proposed to determine kinetic parameters and the values calculated with these methods depend not only on the experimental conditions but also on data treatment procedures. One main purpose of kinetic analysis of solid decomposition is to determine reaction mechanism(s) and to calculate Arrhenius parameters. There are two ways to do this, using either isothermal or non-isothermal kinetic analysis. Wendlandt has summarized the advantages and disadvantages of determining kinetic parameters by non-isothermal methods rather than by conventional isothermal studies [14].

As with any instrumental technique, there are a large number of factors that can affect the nature, precision, and accuracy of TG experimental results. Because of the dynamic nature of the temperature change of the sample a larger number of variables can affect TG measurements. Some authors have discussed in detail the precautions involved in using a thermobalance as well as the importance of many variables involved in TG. Basically, the factors that can influence the mass-change curve of a sample fall

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into two categories: instrumental (furnace heating rate, furnace atmosphere, sample container composition, sample holder geometry and furnace environment) and sample characteristics (sample amount, particle size, thermal conductivity, sample packing and heat of reaction) [15, 16].

In view of the large number of factors that could affect TG determinations factorial designs are very appropriate for their study. A small number of experiments can be run to assess the effect of each factor studied as well as all possible interaction effects involving two or more factors. This is achieved by studying all possible combinations of different factor levels for all factors. Conventional univariate experiments are incapable of measuring interaction effects and normally are more time consuming than multivariate factorial designs that require a smaller number of experiments to optimize results [17–20].

It has often been reported in the literature that the values of the kinetic parameters of thermal decomposition, the activation energy, E, the pre-exponential factor, A, and the reaction extent function, $f(\alpha)$, depend on experimental conditions. Many papers illustrate this problem and show the influence of sample mass, atmosphere, gas flow, crystallite size, and other factors on the shape of kinetic curves measured for the decomposition of solids or reactions of solids with a gas (oxidation, reduction) [21]. Traditionally pharmaceutical formulations are developed by changing one variable at a time. This method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to optimize measurements using this classical technique since the interaction effects of variables can not be assessed in this way. The aim of this work is to demonstrate the usefulness of the factorial design as a tool for the rapid exploration of thermal responses as a function of the sample mass (4 or 8 mg), furnace environment (dry or humid), atmosphere (nitrogen or air) and crucible type (alumina or platinum). In the last years we have been studying some aspects involving the zidovudine [22–24] and in this work the thermal stability and kinetics investigation of degradation was carried out by applying Ozawa's method [25] to the thermogravimetry of a commercial sample of zidovudine (AZT).

Experimental

An AZT pharmaceutical capsule (Retrovir® – 100 mg) was obtained from Glaxo Wellcome Pharmaceutical Industry, lote: 7A2225. Since the effects of four factors are to be investigated simultaneously 2^4 (i.e. 16) experiments have to be performed at all possible combinations of the factor settings. In order to perform an error analysis the different sets of factor levels were run randomly. DSC curves were obtained in a DSC-50 cell (Shimadzu) using aluminum crucibles with about 2 mg of samples, under dynamic nitrogen atmosphere (5 mL min^{-1}) and with a heating rate of 10°C min^{-1} in the 25 to 600°C temperature range. The DSC cell was calibrated with indium (*m.p.*=156.6°C; ΔH_{fus}=28.54 J g^{-1}) and zinc (*m.p.*=419.6°C). TG/DTG curves were obtained with a model TGA 50 (Shimadzu) thermobalance in the 25–900°C temperature range and employing heating rates of 2.5, 5.0, 7.5, 10 and 15°C min^{-1} for dynamic experiments, run using air and nitrogen atmospheres (50 mL min^{-1}), with sample masses of 8.0 and 4.0 mg, in platinum and alumina crucibles and with dry and humid furnace environments. The activation energy was defined from the TG data using kinetic analysis (Shimadzu software) based on Ozawa's method for 5% of mass loss in the first step of thermal decomposition.

Results and discussion

The thermoanalytical profile showed by AZT capsule formulation is presented in Fig. 1. The DSC curve shows, between 25 and 130°C, two endothermic events. The first event is characteristic of the release of water molecules and the second event is due to melting process of AZT (melting point at a temperature of 121°C). After this event thermal decomposition of material is observed in the following temperature ranges: 175–270 (exothermic), 270–305 (endothermic) and 305–450°C (exothermic). The TG/DTG curves obtained at a heating rate of 10°C min^{-1}, using air atmosphere (50 mL min^{-1}), 8.0 mg sample mass, in alumina crucible and dry furnace environment of dynamic air atmosphere (50 mL min^{-1}) indicate that the thermal decomposition process of AZT occurs in five stages in the following temperature ranges with the corresponding mass losses: 25–130°C (Δm=3.67%), 195–270°C (Δm=15.95%), 270–350°C (Δm=38.80%), 350–400°C (Δm=10.40%)

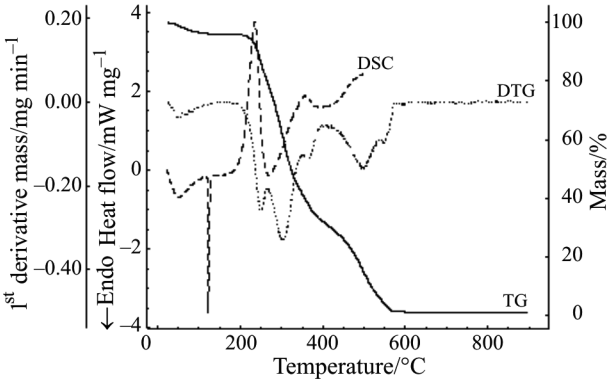

Fig. 1 DSC and TG/DTG curves of AZT capsule formulation at a heating rate of 10°C min^{-1}, obtained using dynamic air atmosphere (50 mL min^{-1}), ~8.0 mg sample mass, alumina crucible and a dry furnace environment

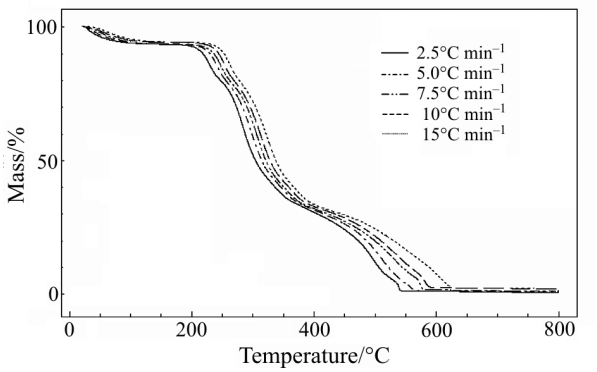

Fig. 2 Overlaid TG curves of the contents of AZT capsules obtained using heating rates at 2.5, 5, 7.5, 10 and 15°C min^{-1}, dynamic air atmosphere (50 mL min^{-1}), ~8 mg sample mass, alumina crucible and a dry furnace environment

and 400–590°C (Δm=29.74%). These events are characteristic of the release of water molecules, thermal decompositions (three stages), followed by the elimination of carbonaceous materials.

Figure 2 shows, as an example, the TG curves for different heating rates of the AZT capsules obtained with air atmosphere (50 mL min^{-1}) and an 8.0 mg sample mass in an alumina crucible with a dry furnace environment. The overlay plots there show the heating rate dependence (effect) on the rate of thermal decomposition. This figure shows that the temperature curves shift to higher values and the following rate increases. This result indicates that the heating rate influences temperature distribution inside the sample and instrument detection.

The method established by Ozawa is an integral method for determining the activation energies in dynamic heating experiments. The activation energy can be obtained from a plot of logarithms of heating rates, A, as a function of the inverse of temperature, $1/T$, for a constant $G(x)$, where $G(x)$ is the integrated form of the conversion dependence function, $f(\alpha)$. Figures 3 and 4 show the plots obtained and the $G(x)$ graphic function of the inverse temperature for AZT capsules demonstrating good correlation at the five heating rates. These types of plots show a better linear relationship than those taken from the data range of TG curves organized in terms of the plotted range, the initial and final mass range used, and the reaction order assumed.

Table 1 shows the definition of the two levels investigated for each of the four factors. The use of the – and + signs conveniently discriminates the different levels for each factor and does suggest that one level is preferred over another. Besides the model-fitting analysis, the variation in $f(\alpha)$ as a function of α under non-isothermal conditions and the relation of percentage mass loss to the kinetic energy of the thermal decomposition process results in variations in activation energies between 107 and 132 kJ mol^{-1} for the different conditions in Table 1. In general terms the decomposition mechanisms for AZT content of capsules showed a possible zero-order mechanism.

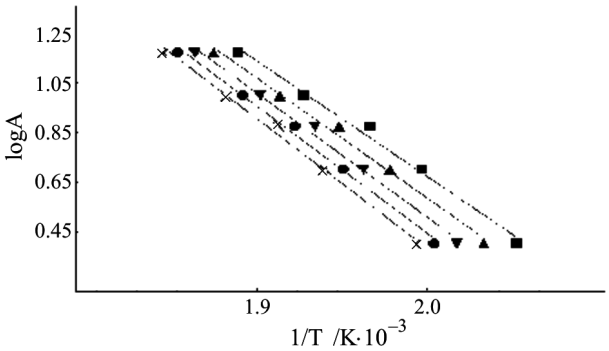

Fig. 3 Ozawa's plot of the contents of AZT capsules

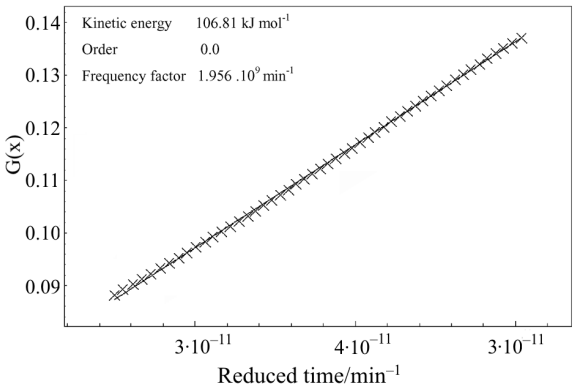

Fig. 4 $G(x)$ graphic function of the inverse temperature of the contents of AZT capsules

Besides the TG curves the last column of Table 2 contains the activation energies determined at all 16 possible combinations of the two levels of each factor.

Main and interaction effects are simply contrasts between averages calculated at the high (+) and low (–) levels of each factor,

$$\text{Effect} = \overline{R}_{+} - \overline{R}_{-}$$

Each average is composed of eight contributions. For the main effects the signs in the above equation correspond to the signs of the appropriate factor column. Note that there are eight plus and minus signs

Table 1 2^4 factorial design (16 experiments) for the determination of kinetic parameters of the thermal decomposition of AZT by TG

Factor	–	+
Atmosphere	Nitrogen	air
Sample mass	4 mg	8 mg
Crucible	Platinum	Alumina
Furnace ambient	Dry	Humid

Table 2 DTG peak temperatures and activation energies for the 2^4 factorial design experiments for the thermal decomposition of AZT using a non-isotherm method

Condition	1	2	3	4	$T_{peak\ DTG}$/°C	E_a/kJ mol^{-1}
N_2 4 al dry	–	–	–	–	255.8	111*
N_2 8 al dry	+	–	–	–	257.8	119
Air 4 al dry	–	+	–	–	257.2	111*
Air 8 al dry	+	+	–	–	253.4	117*
N_2 4 Pt dry	–	–	+	–	255.4	107
N_2 8 Pt dry	+	–	+	–	251.3	124
Air 4 Pt dry	–	+	+	–	256.7	129
Air 8 Pt dry	+	+	+	–	249.0	126*
N_2 4 al hu	–	–	–	+	259.2	107
N_2 8 al hu	+	–	–	+	251.9	113
Air 4 al hu	–	+	–	+	254.2	111
Air 8 al hu	+	+	–	+	248.7	124
N_2 4 Pt hu	–	–	+	+	249.8	119
N_2 8 Pt hu	+	–	+	+	248.6	131
Air 4 Pt hu	–	+	+	+	248.9	132
Air 8 Pt hu	+	+	+	+	247.4	130

N_2 – nitrogen, Air – synthetic air, Pt – platinum, al – α-alumina, hu – humidity and dry – dry; *Average values of the experiments in duplicate; individual values are (– – – –) 106, 116; (– + – +), 96, 126; (+ + – –), 107, 126 and (+ + + –), 127, 125. A ±13.1 pooled measurements error is obtained from the duplicates

in each column of the factorial design. The (+) and (–) signs in this equation for the calculation of the interaction effects are determined by simply multiplying the signs of the factors involved in the interaction. There will always be eight positive and eight negative products for each interaction effect. The factorial design is an orthogonal one. For this reason it is possible to determine individual effect values whether they be main or interaction ones.

The effect values are compiled in Table 3 along with the average of the 16 experimental activation energies. In addition to the four main effects there are six possible binary interaction effects, four ternary ones and one possible quaternary effect. Of course not all of these effects really exist and the ones with smaller absolute values are probably not zero owing to error propagated from the experimental errors in the activation energy values in Table 2. The crucible type and atmospheric main effects have the largest effect values. The other effects have absolute values that are lower. However furnace environment and the ternary interaction involving sample mass, crucible type and furnace environment are not that much lower.

Significant effect values can be determined without performing replicate experiments and rigorously estimating errors by using cumulative probability graphs such as the one presented in Fig. 5 for the effect values of Table 3. The effect values are plotted on the abscissa and the ordinate values are expected cu-

Table 3 Main and interaction effects of the 2^4 factorial design for the thermal decomposition of AZT. (Units of kJ mol^{-1})

Average	119.0558
Main effects	
1 atmosphere	7.8884[a]
2 sample mass	5.1875
3 crucibles	11.2143
4 ambient	5.6875
Interaction between two factors	
1 2	–2.6875
1 3	–2.0625
1 4	–2.6875
2 3	3.6384
2 4	3.6116
3 4	0.9866
Interaction between three factors	
1 2 3	–5.9866
1 2 4	–1.1116
1 3 4	1.8616
2 3 4	–6.4375
Interaction between four factors	
1 2 3 4	–0.5

[a]Effect values have standard errors of ±5.8. This value is calculated from the pooled variance of the four duplicate results in Table 2

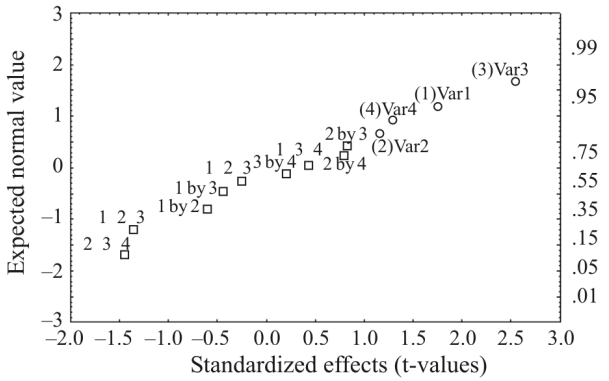

Fig. 5 Cumulative probability graph for the 2^4 factorial design effects on the thermal decomposition of contents of AZT capsules; □ – interactions, ○ – main effects and other effects

mulative probabilities of occurrence for random variables taken from a normal distribution. Since the experiments were performed in random order one can expect that effect values only caused by random experimental errors would fall on a straight line centered on the zero abscissa value in the graph. The plot in Fig. 5 shows that the point corresponding to the crucible type clearly falls off the straight line. It is not clear whether the point representing the atmospheric effect really falls on this line or not.

To determine the significance of the effects of the four-factor design, four measurements were made in duplicate from which a standard error in the effect values of ±5.8 was calculated. This corresponds to a 95% confidence level error of ±16.1. At this confidence level no effect value is significant.

Conclusions

This study demonstrated the use of a factorial design for the evaluation of the experimental conditions for the determination of kinetic parameters using thermal analysis. This statistical technique is an excellent tool providing a means whereby the effects involved in a given experiment can be simultaneously estimated and tested for importance and allows scientists to examine more than one variable at a time while performing a smaller number of experiments than in univariate techniques. The TG analysis demonstrated no significant differences between the results of activation energies for different experimental conditions.

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