J Therm Anal Calorim
DOI 10.1007/s10973-017-6279-3

Evaluation of activation energy conformity derived from model-free non-isothermal predictions and Arrhenius isothermal results

The case of hydrochlorothiazide–lactose reaction

Faranak Ghaderi[1,2] · Mahboob Nemati[1,3] · Mohammad Reza Siahi-Shadbad[3,4] · Hadi Valizadeh[5] · Farnaz Monajjemzadeh[3,4]

Received: 28 September 2016 / Accepted: 6 March 2017

Abstract In this study, the activation energy of HCTZ–lactose interaction was determined and compared to isothermal and non-isothermal methods. DSC data were fitted to different thermal models such as Friedman, Flynn–Wall–Ozawa and Kissinger–Akahira–Sunose, and the activation energy was calculated subsequently. Isothermal studies were performed by heat ovens, and analysis was done using high-performance liquid chromatography technique, and the activation energy (E_a) were calculated according to Arrhenius method. To date, no practical evaluations has been performed in the literature on the conformity of these different heating methods in incompatibility studies. The kinetic data obtained from the isothermal and non-isothermal methods showed no significant difference. The current study demonstrated a good conformity between the isothermal and non-isothermal kinetic results, and thus, it can be suggested that DSC-based kinetic analysis can provide a simple, reliable and fast comparative data in the kinetic evaluation of an incompatibility seen in early stages of preformulation studies. Finally, the advantages and drawbacks of each method are fully discussed.

Keywords Isothermal · Non-isothermal · Thermal analysis · Incompatibility · Drug–excipient · Hydrochlorothiazide

Abbreviations

HCTZ	Hydrochlorothiazide
FWO	Flynn–Wall–Ozawa
KAS	Kissinger–Akahira–Sunose
HPLC	High-performance liquid chromatography
DSC	Differential scanning calorimetry

Introduction

Recent developments in analytical evaluation of drug stability have highlighted the need for fast and reliable predictions. Nowadays, researchers have shown an increased interest in drug–excipient interaction issues. This type of interactions may lead to the drug loss and also the formation of degradation products in the pharmaceutical preparations. The loss of drug potency and the unknown safety of the newly formed degradation products oblige the analyst to avoid any possible interactions by establishing some evaluations in early stages of preformulation studies [1]. Perhaps, lactose is one of the most widely used excipients in pharmaceutical oral dosage forms (tablets) for more than a century. But this valuable excipient acts as a reducing sugar and participates in a nucleophilic reaction with amines known as Maillard reaction.

✉ Farnaz Monajjemzadeh
Monaggemzadeh@tbzmed.ac.ir;
Monajjemzadehf@yahoo.com

1 Food and Drug Safety Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

2 Department of Drug and Food Control, Urmia University of Medical Sciences, Urmia, Iran

3 Department of Pharmaceutical and Food Control, Tabriz University of Medical Sciences, Tabriz 5166414766, Iran

4 Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

5 Department of Pharmaceutics, Tabriz University of Medical Sciences, Tabriz, Iran

Published online: 23 March 2017

Detailed evaluation of hydrochlorothiazide (HCTZ)–lactose Maillard-type interaction has been reported by Harmon et al. [2].

HCTZ (6-chloro-1, 1-dioxo-3, 4-dihydro-2*H*-1, 2, 4-benzothiadiazine-7-sulfonamide) is an amine containing thiazide-type diuretic drug which is often used to treat high blood pressure and edema management due to fluid retention. HCTZ has been marketed as oral dosage form and may be combined with other blood pressure drugs as a single pill to increase the effectiveness [3–6].

Many other pharmaceutically interested agents with amine functional groups in their structure can react with reducing excipients, and thus, this type of interaction has gained great importance in pharmaceutical science in recent years [2, 7].

Kinetic evaluation is a key experiment used to elucidate fundamental information about the rate of a reaction progress, comparison, evaluation and prediction of multiple reactions.

The most conventional method in the kinetic study of a reaction is based on the assay of the unreacted or remained drug using high-performance liquid chromatography (HPLC) technique. This method is very sensitive, precise and reliable but is time-consuming and also so expensive.

The findings of different researchers have suggested differential scanning calorimetry (DSC) for drug–excipient incompatibility evaluation [8–10]. Multiple scanning method at different heating rates by using isoconversional calculation procedures is recently defined for solid-state kinetic studies. Friedman (FR), Kissinger–Akahira–Sunose (KAS) and Flynn–Wall–Ozawa (FWO) methods have been widely used to study the activation energy (E_a) [11, 12].

To date, no practical evaluation has been performed in the literature on the conformity of these different heating methods in incompatibility studies. In this research, the activation energy (E_a) of HCTZ–lactose interaction as a well-known drug–excipient incompatibility reaction was evaluated using non-isothermal and isothermal methods. Activation energy (E_a) derived from each method was calculated according to the models and compared. Finally, the advantages and draw backs of each method are fully discussed.

Materials and methods

Materials

HCTZ was obtained from Unichem (Maharashtra, India); anhydrous lactose was provided from DMV Chemical Co. (Veghel, Netherlands). HPLC grade methanol was purchased from Duksan (Gyeonggi-do, Korea); potassium dihydrogen phosphate (KH_2PO_4) and ortho-phosphoric acid were received from Merck (Darmstadt, Germany).

Methods

DSC

DSC curves were obtained in a differential scanning calorimeter (DSC-60, Shimadzu, Japan) using aluminum pans with about 5 mg of samples including pure drug, pure excipient and their physical mixture in 1:1 mass ratio. Samples were scanned at different heating rates including 2.5, 5, 7.5, 10 and 15 °C min^{-1} in the temperature range of 25–300 °C. TA-60 software (version 1.51) was used for enthalpy calculations.

HPLC

A previously reported stability indicating HPLC method which was capable of quantifying HCTZ in the stressed samples was used [13]. The HPLC analysis was performed on a Knauer HPLC (Berlin, Germany) consisting of a Knauer-controller quaternary pump and a UV detector (Knauer No. E 4310). The separations were conducted by isocratic elution using filtered and degassed mixture of solvents [methanol/phosphate buffer 20 mM (60:40 v/v)] as a mobile phase. Samples (20 µL) were injected into a C18 column (250 mm, 4.60 mm, 5 µm; Beckman, USA) maintained at ambient temperature, and mobile phase flow rate was 1 mL min^{-1}. Detection was performed at 270 nm.

Data were analyzed with EZ Chrome Elite software. The analytical method was validated thoroughly by Bhagwate and Gaikwad [13] according to ICH. Despite utilizing a validated method, the purity of the peak responsible for HCTZ was double checked by PDA (photodiode array) detector. The occurrence of Maillard reaction in all tested samples was confirmed using mass spectrometry (Waters 2695, Milford, MA, USA) and FTIR spectroscopy (Bomem, MB-100 series, Quebec, Canada).

Kinetic study

Non-isothermal DSC kinetic study

DSC curves were analyzed using differential models such as FR method and also integral models such as KAS and FWO methods, and the activation energy of HCTZ–lactose interaction was calculated in non-isothermal condition.

Isothermal Arrhenius kinetic study

HCTZ and lactose binary mixture were prepared in 1:1 mass ratios and according to Serajuddin et al. [14], were added 20% (v/w) water and stored in closed vials at 60, 70, 80 and 90 °C. Sampling was performed at predetermined time intervals and analyzed by HPLC technique. The

residual drug was determined using a validated HPLC method 7, 14, 21 and 28 days after incubation at 60, 70, 80 and 90 °C and calculated from the calibration curve. Then, the order of reaction was calculated. Activation energy (E_a) and preexponential factor (A) were determined by means of the slope and intercept of Arrhenius plot. Data were fitted to different solid-state kinetic models for HCTZ–lactose interaction.

Statistical calculations

Analysis of variances was done using ANOVA test (SPSS statistics 17.0) for mean comparison whenever required.

Results and discussion

Analytical methods

DSC

DSC is one of the most commonly used techniques to study the drug–excipient compatibility in preformulation stage and also present important information about the properties of materials such as stability, polymorphism, kinetic analysis and phase transitions [15, 16].

When two substances are mixed, the purity of each will be reduced and generally slightly lower melting endotherms may result. If the solid–solid interaction is extremely weak or nonexistent, the reduction of the melting point is usually negligible. Literature review provides different examples for this rule [17–24]. Hydroquinone compatibility with ethylenediaminetetraaceticacid (EDTA) represents a slight shift in the melting endotherm of the drug in the binary mixture, which is considered as no interaction. In the other study, aspirin and magnesium stearate incompatibility was concluded by a new peak generation along with melting endotherm disappearance [24].

In this study, the preferred drug to excipient ratio was selected as 1:1 w/w. This ratio is a common selection in incompatibility studies.

HCTZ melting endotherm was only observed at higher drug ratios (10:1, drug/excipient) (data not shown). Melting peak of HCTZ in lower drug ratios such as 1:1 and 1:10 in drug–excipient binary mixtures completely disappeared which can be attributed to the complete interaction of the components. A new peak was seen in about 245 °C. The new peak intensity was also different in different ratios. The most intense peak was seen in higher excipient ratio (1:10). This finding can be explained by the reaction progress in the binary mixtures. This is in accordance with molar ratios of the corresponding mass ratios. The calculated mole ratios for 1:1, 1:10 and 10:1 mass ratios of drug to excipient is equal to about 1.2:1, 11.5:1 and 0.12:1, respectively.

Figure 1 presents the DSC curves of pure drug, pure excipient and drug–excipient mixture at (1:1 mass ratio).

According to Fig. 1a, HCTZ and lactose presented their melting point at 274.32 and 239.45 °C, respectively. The melting endothermic peak of HCTZ disappeared in the HCTZ–lactose binary mixture, which may refer to drug–excipient incompatibility (Fig. 1a).

As a result of DSC curves (Fig. 1b), the heating rate has significant effect on the temperature range and the shape of thermoanalytical curves [25].

HPLC

To date, various HPLC methods have been developed and introduced in kinetic evaluation of different chemical reactions [26, 27].

Although Harmon et al. [2] have previously reported a HPLC method for the HCTZ–lactose interaction monitoring, the authors could not get satisfactory peak shapes in several runs. Thus, another stability indicating method for stressed samples was used and its ability to quantify the HCTZ in the presence of the Maillard reaction products was initially examined by peak purity using PDA detector [13]. The resulted peak purity factor revealed the method specificity for this purpose. The utilized stability indicating HPLC method showed no new peak in the Maillard reaction mixtures.

System suitability factors such as tailing factor, capacity factor, column efficiency and mean repeatability (for three concentrations of (10–40 and 80 μg mL^{-1})) were also calculated as, 1.1, 2.03, 252 and 1.8%, respectively.

From each binary mixture, 150 mg samples were thoroughly weighted and dissolved in 50 mL methanol ($n = 3$). Then, the solutions were sonicated for 5 min and filtered through 0.45-μm membrane filter. Samples were diluted with methanol to produce solutions with a nominal HCTZ concentration of 15 μg mL^{-1}. According to the HPLC results, the drug loss was depicted by a reduction in the peak area. The drug loss can be attributed to Maillard reaction which has been demonstrated previously by Harmon et al. [2].

DSC is mainly a screening technique indicating the possibility of an assumed incompatibility among drug and excipients in preformulation studies without providing complementary data regarding the type of incompatibility (either physical or chemical). Thus, further MS and FTIR analyses were applied to confirm the formation of the condensation product due to the Maillard reaction in analyzed samples.

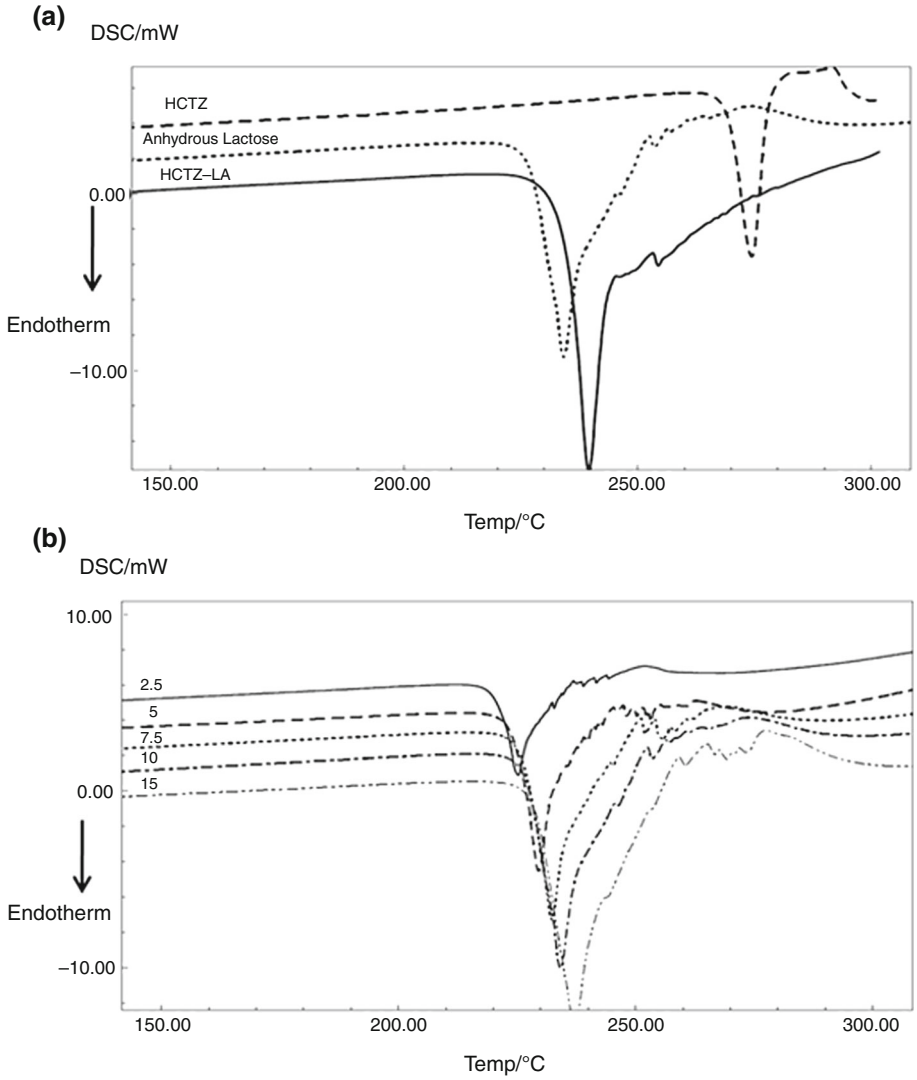

Fig. 1 DSC curves of **a** HCTZ, anhydrous lactose and HCTZ–anhydrous lactose (1:1 w/w) binary mixture ($\beta = 10$). **b** HCTZ–anhydrous lactose physical mixture with 1:1 mass ratio at different heating rates ($\beta = 2.5$, 5, 7.5, 10 and 15)

For non-isothermally heated samples, the type of the incompatibility was rechecked by stopping the DSC analysis in peak temperature point and moving out the heated sample through the pan. FTIR and mass results are presented in Fig. 2.

The Maillard reaction confirmation in the tested samples in various conditions was performed by FTIR and mass spectrometry analysis. The mass results showed an *m*/*z* value at 622.1 and 622.3, respectively, for HCTZ–LA isothermally and non-isothermally heated binary samples, which is related to $[M+H]^+$ HCTZ–lactose condensation product. This mass value is in agreement with Harmon et al. [2]. Meanwhile, the FTIR spectra showed a major reduction in amine peak for HCTZ–lactose-tested samples in both isothermally and non-isothermally heated samples compared with pure drug, which can be attributed to the Maillard incompatibility and consequent amine loss (Fig. 2).

Kinetic study

Non-isothermal DSC kinetic study

Various researchers have defined multiple scanning method at different heating rate as a fast DSC method in kinetic studies [28]. Literature review showed that no practical evaluations have been performed on the conformity of different heating methods in drug–excipient incompatibility studies [12, 29].

The activation energy of HCTZ–lactose mixture interaction are calculated by FR [30], KAS and FWO methods [31]. Table 1 summarizes the main thermal equations for the mentioned methods. All parameters have been defined as follow:

α is defined as conversion degree and can be calculated by the following formula (Eq. 1):

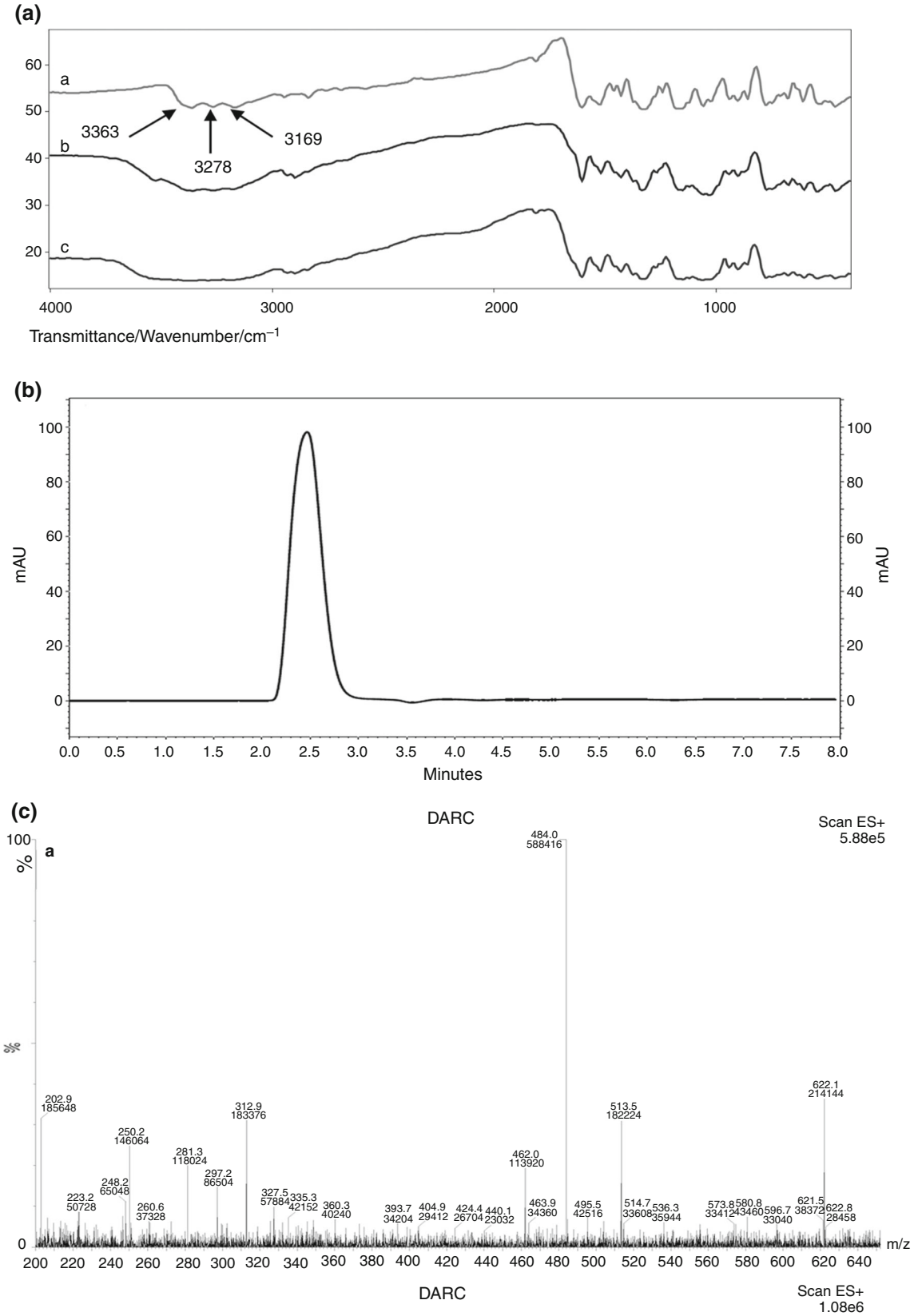

Fig. 2 Instrumental analysis of samples **a** FTIR spectra of (*a*) pure HCTZ, (*b*) HCTZ–LA isothermally heated binary samples, (*c*) HCTZ–LA non-isothermally heated binary sample, **b** HPLC chromatogram of binary samples and **c** mass results of (*a*) HCTZ–LA isothermally heated binary samples, (*b*) HCTZ–LA non-isothermally heated binary sample

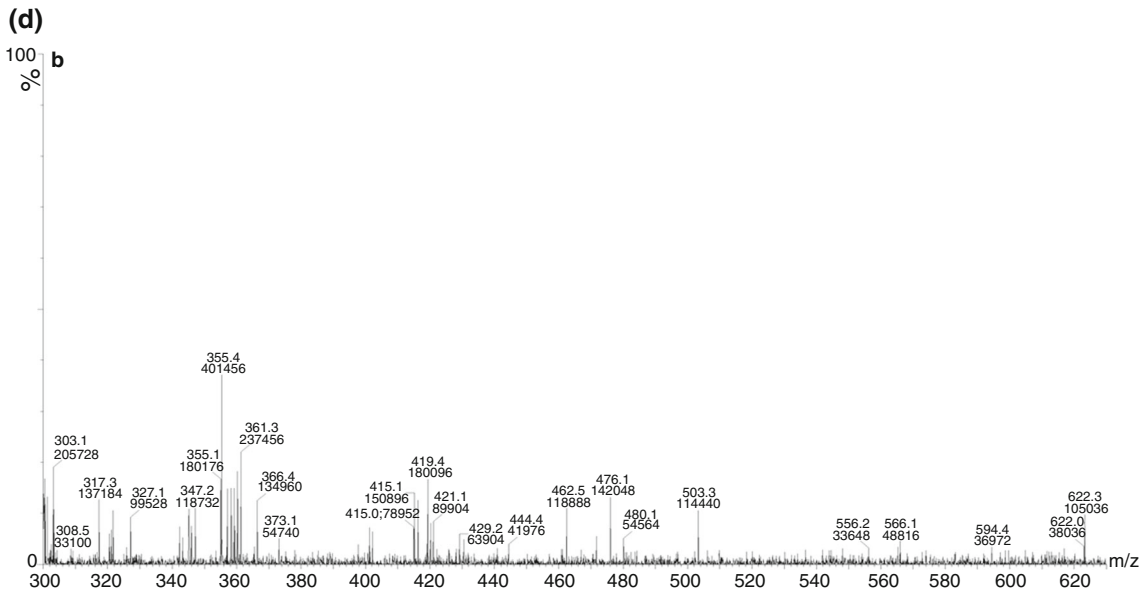

Fig. 2 continued

Table 1 Friedman (FR), Flynn–Wall–Ozawa (FWO) and Kissinger–Akahira–Sunose (KAS) methods equations

Method	Equation
Friedman (FR)	$\ln(\beta \frac{d\alpha}{dT}) = \ln[A \cdot f(\alpha)] - (\frac{E}{RT})$
Flynn–Wall–Ozawa (FWO)	$\ln \beta = \ln \frac{A \cdot E}{R \cdot f(\alpha)} - 5.331 - 1.052 \cdot \frac{E}{RT}$
Kissinger–Akahira–Sunose (KAS)	$\ln(\frac{\beta}{T^2}) = \ln \frac{A \cdot R}{E \cdot f(\alpha)} - \frac{E}{RT}$

$$a = \frac{\mathrm{AUC}^{\mathrm{T}}_{\mathrm{T_{onset}}}}{\mathrm{AUC}^{\mathrm{T_{Endset}}}_{\mathrm{T_{onset}}}} \quad (1)$$

where $\mathrm{AUC}^{\mathrm{T}}_{\mathrm{T_{onset}}}$ represents area under curve of the thermograms peak from peak onset temperature to temperature T, whereas $\mathrm{AUC}^{\mathrm{T_{Endset}}}_{\mathrm{T_{onset}}}$ is area under the DSC curve of the curves peak from peak onset temperature to end of peak (T_{end}).

If α is kept constant and various heating rates (β) were applied, the plot of $\ln(\beta \cdot \frac{d\alpha}{dT})$ versus ($1/T$) is linear and Friedman plot will be obtained. The values of the activation energy (E_{a}) were calculated from the slopes of the straight lines in Fig. 3 for HCTZ–lactose and are presented in Table 2.

HCTZ–lactose FWO diagrams are shown in Fig. 4. It is apparent from Fig. 4 that a linear relationship is present between lnβ and ($1/T$). Activation energy (E_{a}) was obtained from the slopes of the straight lines and is listed in Table 2.

The values of ($\ln\beta/T^2$) were plotted versus $1/T$ in KAS method and are shown in Fig. 5. Activation energy (E_{a})

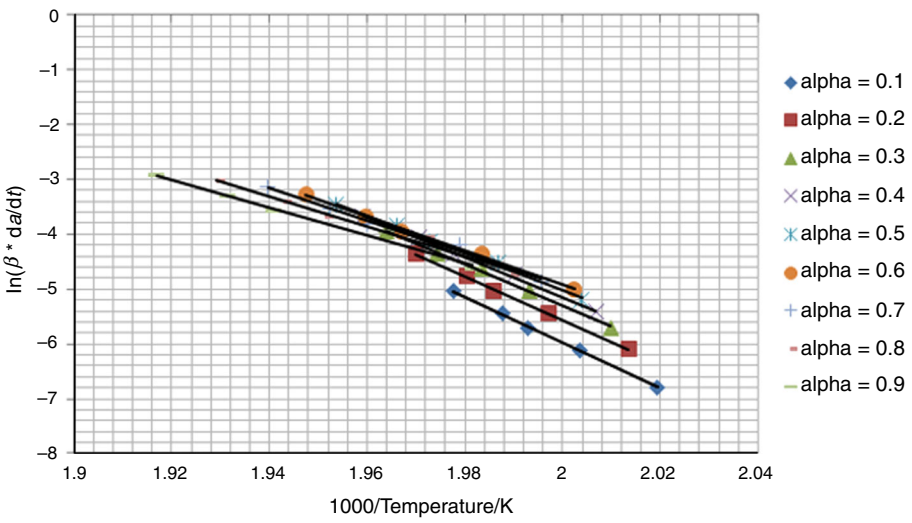

Fig. 3 FR plot for HCTZ–lactose at different heating rates and various conversion degrees

was calculated from slop of the straight lines and is listed in Table 2.

According to Table 2, the calculated mean value for the activation energies resulted from different methods are in a good agreement with each other (P value 0.414).

Isothermal Arrhenius kinetic study

While studying a reaction kinetic, it is important to evaluate the rate at which it occurs and the order of the reaction. Except for zero-order reaction, the rate of a chemical reaction at a fixed temperature is related only to the concentrations of the reactants. Usually, one or more of the reactants affect the rate of the reaction and sometimes products may decrease or increase the rate of the reactions [32].

Reaction orders are only defined and calculated experimentally. Chemical reactions are often categorized as zero-order, first-order, second-order, mixed-order or higher-order, but they may also be seldom, fractional or negative. In general, first-order reactions are most commonly seen ones [33, 34].

The Arrhenius equation is one of the most important relationships for the temperature dependence of reaction rates. The equation was proposed by Svante Arrhenius in 1889, from the result of his direct observations [35, 36].

The Arrhenius equation and non-exponential form of this equation that is often more convenient to use are given bellow as Eq. 2 and 3:

$$k = A\mathrm{e}^{\frac{-\mathrm{E}}{\mathrm{RT}}} \tag{2}$$

$$\ln k = \ln A - \frac{E}{RT} \tag{3}$$

where A is preexponential factor, e is a constant (2.7281), E is the activation energy, R is the gas law constant: 8.314 J mol^{-1} K^{-1}, T is the temperature (K).

Therefore, when a reaction has a rate constant that follows Arrhenius' equation, a plot of ln (k) versus $\frac{1}{T}$ gives a straight line, whose slope and intercept of the Arrhenius plot can be used to calculate the activation energy (E_a) and A. The activation energy (E_a) is the minimum energy that is required for a chemical system with potential reactants to form a chemical reaction.

In this study, the amount of the residual HCTZ was determined using calibration curve [conc. $= 7 \times 10^{-9}$ (peak area) + 0.0017 ($r^2 = 0.9939$)] and the reaction order was determined.

As shown in Fig. 6, the natural logarithm of a reactant concentration plot versus time is linear.

Thus, it can be concluded that HCTZ–lactose interaction in solid state is a first-order reaction and the values of reaction rate coefficient (k) were calculated from the slope

Table 2 Activation energy values for HCTZ–lactose obtained by the Friedman, Flynn–Wall–Ozawa and Kissinger–Akahira–Sunose (KAS) methods

Method	E/kJ mol^{-1}, for conversion degree, α									Mean value
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	
FR	292.51 ± 10.60	282.87 ± 10.07	277.44 ± 10.89	273.90 ± 8.62	271.24 ± 12.37	254.77 ± 4.1	240.51 ± 11.86	219.40 ± 12.02	216.55 ± 9.48	258.80 ± 7.90
FWO	295.5 ± 6.36	292.12 ± 11.14	285.8 ± 10.86	283.54 ± 9.80	275.32 ± 7.07	263.21 ± 4.13	248.99 ± 11.82	227.69 ± 12.30	225.11 ± 9.50	266.27 ± 7.12
KAS	306.76 ± 9.56	282.55 ± 10.53	276.70 ± 10.89	273.13 ± 9.89	270.87 ± 12.90	254.08 ± 4.12	239.85 ± 11.82	218.78 ± 11.89	215.97 ± 9.70	259.84 ± 8.02

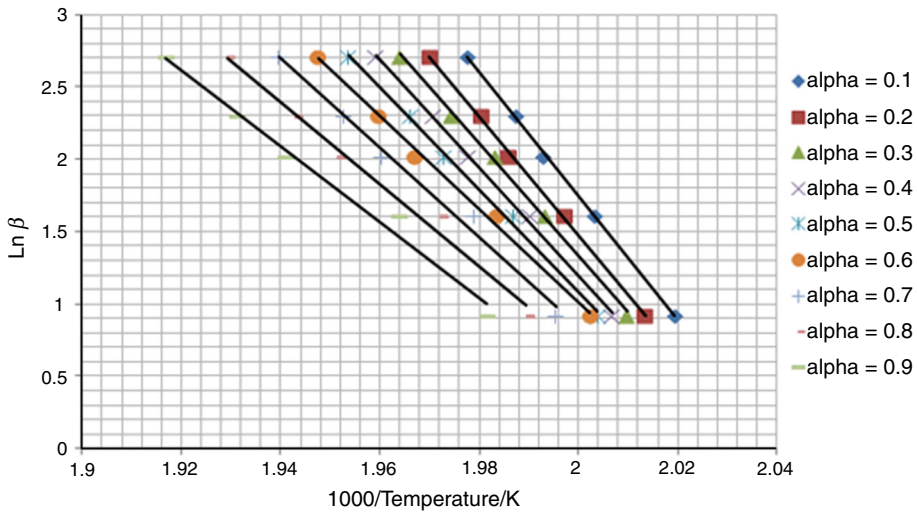

Fig. 4 FWO diagrams for HCTZ–lactose at different heating rates and various conversion degrees

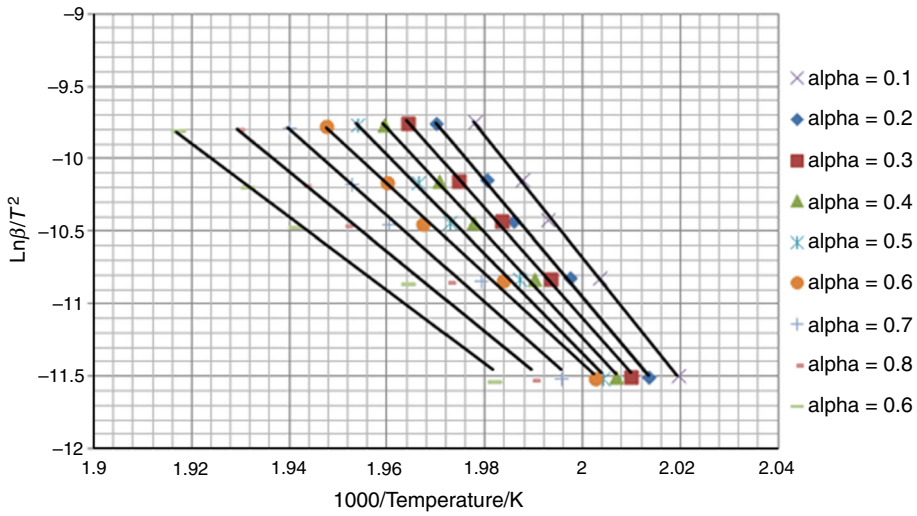

Fig. 5 KSA diagrams for HCTZ–lactose at various heating rates and different conversion degrees

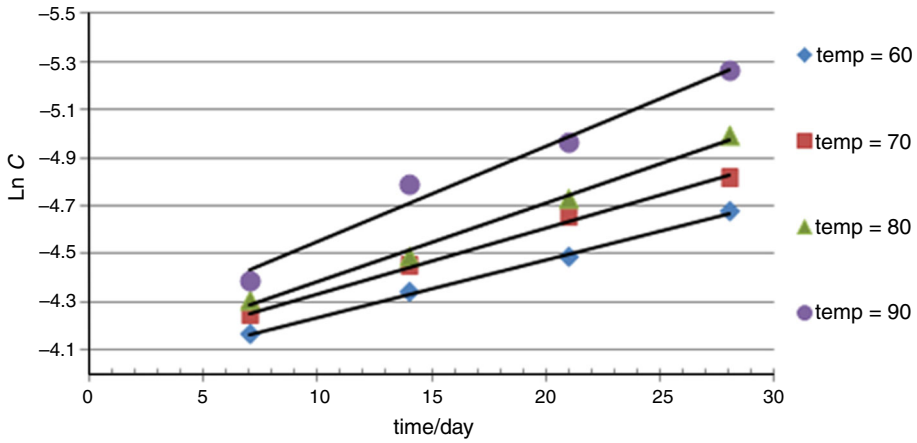

Fig. 6 First-order reaction plot of HCTZ–lactose binary mixture at 1:1 mass ratio and 20% added water after 7, 14, 21 and 28 days incubation at 60, 70, 80 and 90 °C

of these plots for mentioned temperatures and are presented in Table 3.

Different solid-state kinetic models have been used by researchers previously [37]. Generally, the models are based on different theories such as nucleation, geometrical contraction and reaction order.

Nucleation model is based on the formation and growth of nuclei which is the rate-limiting step in the reaction.

Table 3 Values of reaction rate constants (k) and RSQ obtained from the first-order reaction plot of HCTZ–lactose mixture after 7, 14, 21 and 28 days incubation at 60, 70, 80 and 90 °C

Temperature/°C	k	R^2
60	0.0238	0.9976
70	0.0273	0.9976
80	0.0329	0.9945
90	0.0397	0.9769

The geometrical contraction model assumes that nucleation occurs instantly on the surface of the crystal. The rate of reaction is limited by interfacial progress.

In order-based models which are the simplest models, "the reaction rate is proportional to concentration, amount or fraction remaining of reactants raised to a particular power which is the reaction order" [38–43].

Table 5 lists the different subgroups for the mentioned models.

Table 4 Parameters obtained from the fitting of the reaction rate data at 60, 70, 80 and 90 °C to various solid-state kinetic models

Models	Temperature/°C	60	70	80	90
Nucleation models					
Power law (P2)	Intercept	−0.12794	−0.10481	−0.11862	0.524717
	Slope	0.028411	0.031025	0.033724	0.010031
	R^2	0.921442	0.846783	0.857574	0.965565
Power law (P3)	Intercept	−0.10887	−0.08427	−0.09291	0.658658
	Slope	0.032805	0.034689	0.036677	0.007405
	R^2	0.843942	0.777747	0.786024	0.976688
Power law (P4)	Intercept	−0.09234	−0.06945	−0.07556	0.734146
	Slope	0.035172	0.036631	0.038196	0.005845
	R^2	0.793128	0.737745	0.744258	0.967189
Avarami–Erofe'ev (A2)	Intercept	−0.15911	−0.14369	−0.17551	0.49897
	Slope	0.031963	0.036195	0.040909	0.018624
	R^2	0.947268	0.887385	0.908907	0.964079
Avarami–Erofe'ev (A3)	Intercept	−0.13178	−0.11142	−0.1314	0.653234
	Slope	0.035536	0.038502	0.041798	0.012885
	R^2	0.871369	0.812473	0.83145	0.959345
Avarami–Erofe'ev (A4)	Intercept	−0.11031	−0.09019	−0.10453	0.734938
	Slope	0.037371	0.039637	0.042166	0.009848
	R^2	0.817519	0.766456	0.78221	0.960691
Geometrical contraction models					
Contracting area (R2)	Intercept	−0.07267	−0.07445	−0.096	0.094551
	Slope	0.010064	0.012625	0.01545	0.011108
	R^2	0.994828	0.98155	0.991609	0.974394
Contracting volume (R3)	Intercept	−0.05097	−0.05331	−0.06996	0.05523
	Slope	0.006971	0.00885	0.010971	0.008486
	R^2	0.997348	0.98535	0.984751	0.961706
Reaction order					
Zero-order	Intercept	0.017354	0.016109	0.015711	0.013976
	Slope	−0.00029	−0.0003	−0.00032	−0.00033
	R^2	0.995267	0.984492	0.988835	0.933545
First-order	Intercept	−3.99933	−4.06259	−4.05391	−4.05391
	Slope	−0.02387	−0.02739	−0.03296	−0.03975
	R^2	0.9977	0.997656	0.994523	0.97691
Second-order	Intercept	49.22977	50.80962	44.94343	44.52286
	Slope	2.004426	2.583609	3.49575	5.111001
	R^2	0.987248	0.995845	0.971435	0.97102

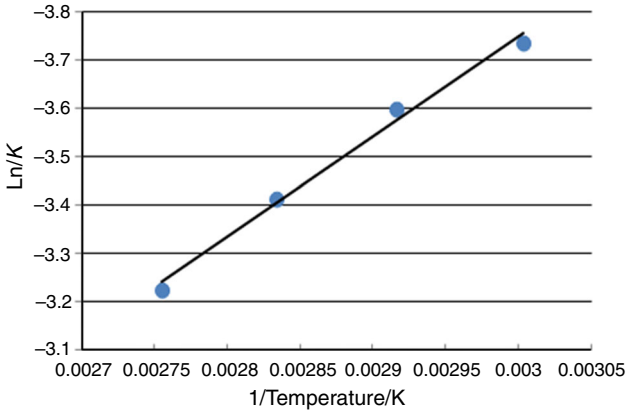

Fig. 7 Arrhenius plot of HCTZ–lactose binary mixture at 1:1 mass ratio

Table 5 Kinetic parameters of HCTZ–lactose binary mixture at 1:1 mass ratio obtained by conventional isothermal Arrhenius method

E_a/kJ mol^{-1}	Ln A	$K^{25\ °C}$	$T_{1/2}^{25\ °C}$/day
254.31	2.46	0.0116	59.5

$K^{25\ °C}$ reaction rate constant at 25 °C

$T_{1/2}^{25\ °C}$ (day) the time required for 50% of the reaction progress at 25 °C

HCTZ loss data were correlated to different kinetic models, and the best fit was accomplished by first-order reaction. Data are presented in Table 4.

Activation energy (E_a) and preexponential factor A were obtained from the slope and intercept of Arrhenius plot, respectively, which is the line generated by regressing ln (k) versus $1/T$ by the use of a least squares linear regression (Fig. 7), and the activation energies (E_a) of the interaction were determined and are presented in Table 5.

The activation energy obtained by non-isothermal DSC kinetic method and conventional HPLC isothermal Arrhenius method for HCTZ decomposition in solid state are 261.63 and 254.31, respectively. Interestingly, the activation energies obtained from two methods are in a good agreement (P value 0.404).

Therefore, DSC-based kinetic analysis can be used instead of conventional isothermal HPLC method which is sensitive and reliable but is time-consuming and expensive. Data accusation will be delayed to reach an acceptable progress in the degradation reaction, even at stress conditions. Method setup, several injections and large sample sizes are the other main shortcomings of common HPLC-based kinetic investigations. Non-isothermal DSC kinetic evaluation offers significant advantages in saving both time and material, and this is valuable where available amount of active pharmaceutical (API) ingredient is too low.

Conclusions

The kinetics of a well-known HCTZ–lactose incompatibility was evaluated by isothermal and non-isothermal methods.

The advantages of DSC kinetic evaluation in comparison with time-consuming and expensive stability indicating HPLC methods included: fast analysis time, low cost, easy sample preparation and small sample size.

Activation energy of the suggested incompatibility reaction estimated using DSC data at various heating rates was in a good agreement with conventional isothermal HPLC methods.

Therefore, it is suggested to apply the non-isothermal methods as fast and simple techniques in kinetic study of drug–excipient incompatibilities in order to compare or predict the extent of reaction in different conditions, different drugs, different excipients and mixtures.

Acknowledgements This paper was extracted from a PhD thesis (No: 91) submitted to faculty of Pharmacy, Tabriz University of Medical Sciences and financially supported by the same university.

Compliance with ethical standards

Conflict of interest The authors declare no financial or other conflict of interests.

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