JOURNAL OF FOOD AND DRUG ANALYSIS XXX (2016) 1–8

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfda-online.com

Original Article

Physicochemical analysis and nonisothermal kinetic study of sertraline–lactose binary mixtures

Faranak Ghaderi [a,b], *Mahboob Nemati* [a,c], *Mohammad Reza Siahi-Shadbad* [c,d], *Hadi Valizadeh* [e], *Farnaz Monajjemzadeh* [d,c,*]

[a] *Food and drug safety research center, Tabriz University of Medical Sciences, Tabriz, Iran*
[b] *Department of Drug and Food Control, Urmia University of Medical Sciences, Urmia, Iran*
[c] *Department of Pharmaceutical and Food Control, Tabriz University of Medical Sciences, Tabriz, Iran*
[d] *Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[e] *Department of Pharmaceutics, Tabriz University of Medical Sciences, Tabriz, Iran*

ARTICLE INFO

Article history:
Received 25 July 2015
Received in revised form
22 June 2016
Accepted 21 August 2016
Available online xxx

Keywords:
drug stability
kinetics
lactose
sertraline

ABSTRACT

In the present study the physicochemical stability of sertraline with lactose was evaluated in drug-excipient binary mixtures. Different physicochemical methods such as differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy, and mass spectrometry were applied to confirm the incompatibility. The final aim of this study was to evaluate the kinetic parameters using a fast and sensitive DSC method. Solid-state kinetic parameters were derived from nonisothermally stressed physical mixtures using different thermal models such as Friedman, Flynn–Wall–Ozawa, and Kissinger–Akahira–Sunose. Overall, the instability of sertraline with lactose was successfully evaluated. Further confirmation was made by tracking the Maillard reaction product of sertraline and lactose by mass spectrometry. DSC scans provided important information about the stability of sertraline in solid-state condition and also revealed the related thermokinetic parameters in order to understand the nature of the chemical instability.

1. Introduction

Drug product stability can be influenced by formulation components in different aspects such as organoleptic or dissolution changes and chemical degradations. These changes may lead to loss of potency and production of unsafe degradation products. Some of the main factors affecting formulation stability include existence of reactive groups in drug and excipient structures, moisture content, drug/excipient ratio, light, relative humidity, temperature, and packaging [1,2].

Thermal analysis includes a group of techniques in which the properties of the materials can be studied while heating or

* *Corresponding author*. Room 105, Department of Pharmaceutical and Food Control, Tabriz University of Medical Sciences, Daneshgah Ave., Tabriz 5166414766, Iran.
E-mail addresses: Monaggemzadeh@tbzmed.ac.ir, Monajjemzadehf@yahoo.com (F. Monajjemzadeh).
http://dx.doi.org/10.1016/j.jfda.2016.08.003

cooling. These methods have been widely applied for the evaluation of possible interactions in pharmaceutical formulation since 1970 [3,4]. Thermal methods have been applied in different pharmaceutical fields such as selection of a suitable salt form, evaluating the phase-diagrams, active pharmaceutical ingredient -excipient interactions, and to predict the physical changes on processing or during drug storage [5,6]. Calorimetry is a fundamental tool used in pharmaceutical industries which measures heat effects related to phase transition and chemical reaction as a function of temperature. Differential scanning calorimetry (DSC) was developed by E.S. Watson and M.J. O'Neill in 1962 and introduced commercially in 1963. This method is the only method for direct measurement of the enthalpy related to the studied processes [7,8]. DSC provides important data about drug-excipient interactions which can cause significant changes in the chemical properties, stability, solubility, absorption, and safety of drug molecules [4,9,10]. Multiple scan method at different heating rates using isoconversional calculation procedures is a fast and precise method, in order to calculate solid-state kinetic parameters. Friedman (FR), Kissinger–Akahira–-Sunose (KAS) and Flynn–Wall–Ozawa (FWO) methods have been commonly used to study the kinetic parameters in solid state chemical interactions [11,12].

Fourier transform infrared spectroscopy (FTIR) is another reliable and accurate technique which is used in drug stability evaluations based on the formation of new absorption peaks or disappearance of already existing infrared absorptions [13].

Sertraline [(1S,4S)-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine] is an antidepressant and acts by selective serotonin reuptake inhibition. This drug is prescribed for major depression, panic, obsessive–compulsive disorders, social anxiety, and premenstrual dysphoric disorders [14].

Since sertraline is widely formulated and used in depression therapies and it has been previously shown that Maillard reaction is the most probable incompatibility reaction of amine-containing drugs with reducing carbohydrates, it is expected that an incompatibility interaction occurs between sertraline and lactose as a reducing carbohydrate. However, to

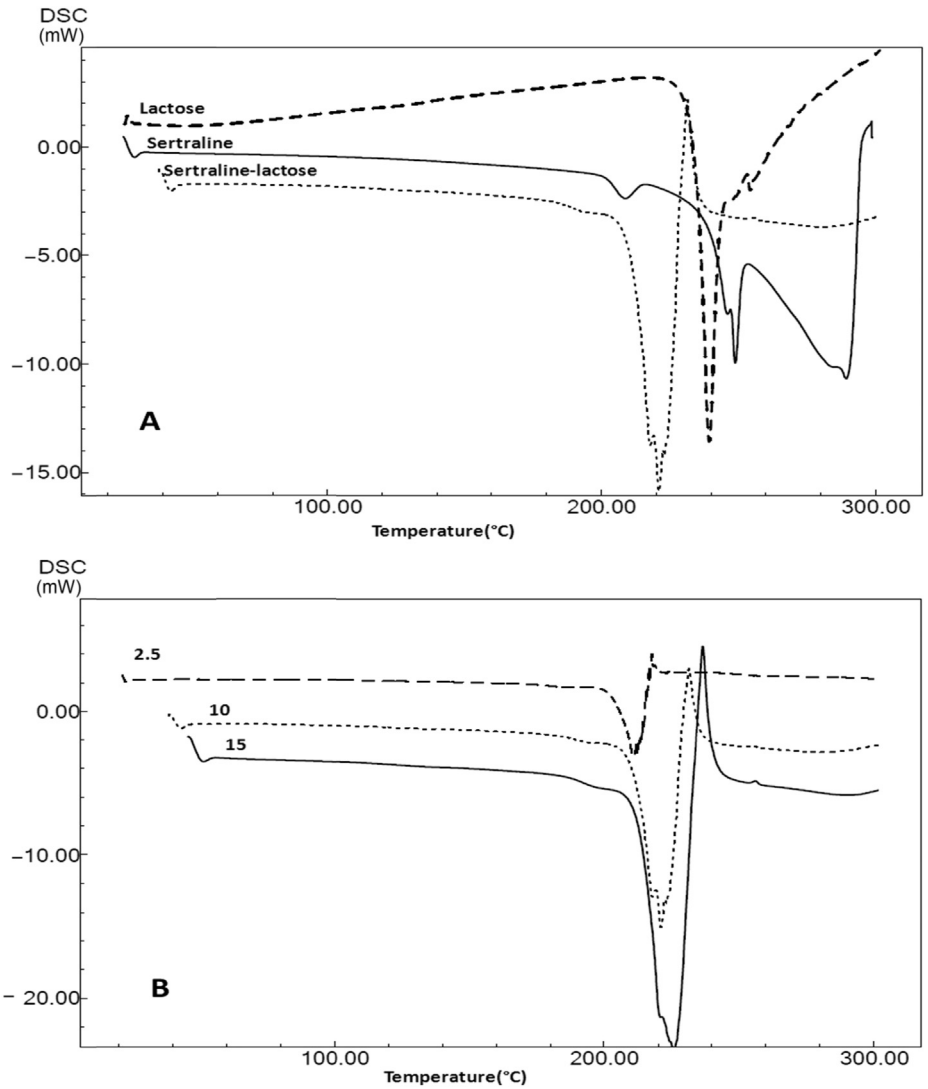


Figure 1 – Selected differential scanning calorimetry (DSC) curves of (A) sertraline, lactose, and sertraline–lactose mixture with 1:1 mass ratio (β = 10) and (B) sertraline lactose 1:1 w/w binary mixture at different heating rates (β = 2.5, β = 10, β = 15).

Please cite this article in press as: Ghaderi F, et al., Physicochemical analysis and nonisothermal kinetic study of sertraline–lactose binary mixtures, Journal of Food and Drug Analysis (2016), http://dx.doi.org/10.1016/j.jfda.2016.08.003

the best of our knowledge, no previous study has been done on the possible instability of sertraline with lactose, up to the date of this investigation [15].

The aim of this research was to evaluate the possible drug instability using different analytical methods (DSC, infrared spectroscopy, and mass spectrometry) and also to obtain basic information about the drug molecule stability in solid state using DSC based fast and reliable thermokinetic parameters.

2. Material and methods

2.1. Materials

Sertraline was obtained from Novin Kavosh Mamatir Co. (Tehran, Iran) and anhydrous lactose was provided from DMV Chemical Co. (Veghal, The Netherlands). NaOH was purchased from Merck (Darmstadt, Germany). All other chemicals were of pure grades and obtained from Merck.

2.2. DSC

A Shimadzu differential scanning calorimeter (Kyoto, Japan) was used for thermal analysis of pure drug, excipient, and their binary mixtures. Binary mixture (10 g) consisted of equal masses of sertraline and lactose was weighed into an amber glass flask; uniform blending was achieved by the tumbling method. Then, 5 mg of each sample was weighed in the DSC aluminum pan and scanned in the temperature range of 25–300°C at various heating rates (2.5°C/min, 10°C/min, and 15°C/min). Enthalpy calculations were performed using TA-60 software (version 1.51) (shimadzu, Japan).

2.3. FTIR

Sertraline and lactose were blended in 1:1 mass ratios, mixed with 20% (v/w) water, and stored in closed vials at 70°C for 3 weeks [16].

FTIR spectra were recorded immediately after mixing and also after storage using the potassium bromide disc preparation method (MB-100 series, Bomem, Quebec, Canada). The spectrum was an average of 10 sequential scans on the same sample and the resolution was kept constant at 4 cm^{-1}. FTIR data was processed by GRAMS/32 version 3.04 (Galactic Industries Corporation, Salem, NH, USA).

2.4. Mass spectrometry

Mass analysis was performed on the Waters 2695 Quadrupole mass system (Milford, MA, USA), at electron-spray ionization mode (positive ionization). These settings were applied to the mass system. The capillary voltage, cone voltage, extractor voltage, RF lens voltage, source temperature, desolvation temperature, desolvation gas flow, and cone gas flow were set at 3.5 V, 30 V, 3 V, 0.10 V, 80°C, 350°C, 500 L/h, and 50 L/h, respectively.

3. Result and discussion

3.1. DSC

DSC can successfully assess the drug-excipient compatibility, as well as provide important data, such as drug purity, drug stability, polymorphic forms, and their stabilities [17–19].

Selected DSC curves of sertraline, lactose, and sertraline–lactose mixture are shown in Figure 1. Thermal behavior of pure drug and pure excipients, as well as the binary mixture, were analyzed in the DSC curves.

According to Figure1A, sertraline presented its melting point at 248.9°C, and revealed a small endothermic peak at 208.8°C which related to the polymorphic form V of sertraline [20].

The endothermic peak of pure anhydrous lactose appeared at 239.1°C ($\beta = 10$).

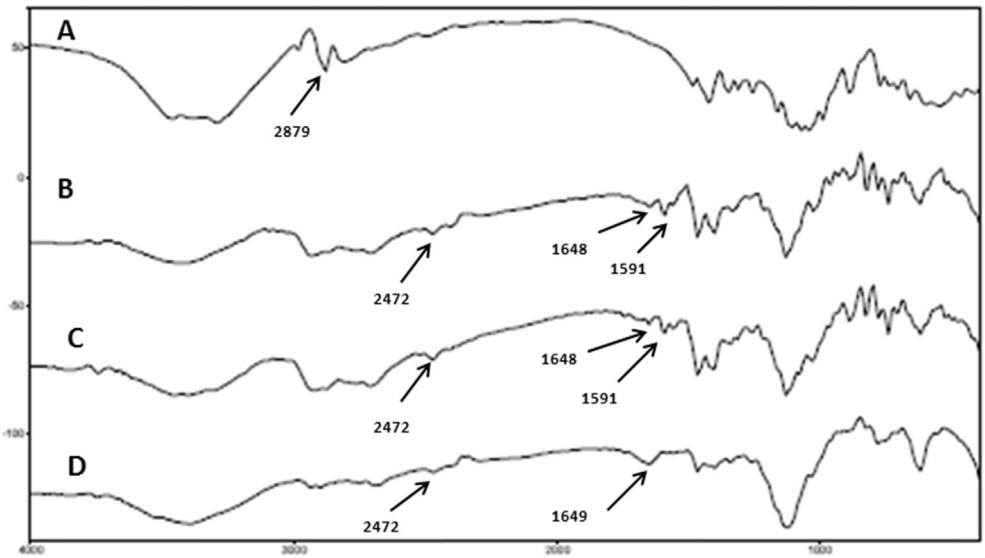


Figure 2 – Fourier transform infrared (FTIR) spectra of (A) lactose, (B) sertraline, (C) sertraline–lactose 1:1 w/w binary mixture immediately after mixing, and (D) binary mixture with 20% added water after 3 weeks incubation at 70°C.

Please cite this article in press as: Ghaderi F, et al., Physicochemical analysis and nonisothermal kinetic study of sertraline–lactose binary mixtures, Journal of Food and Drug Analysis (2016), http://dx.doi.org/10.1016/j.jfda.2016.08.003

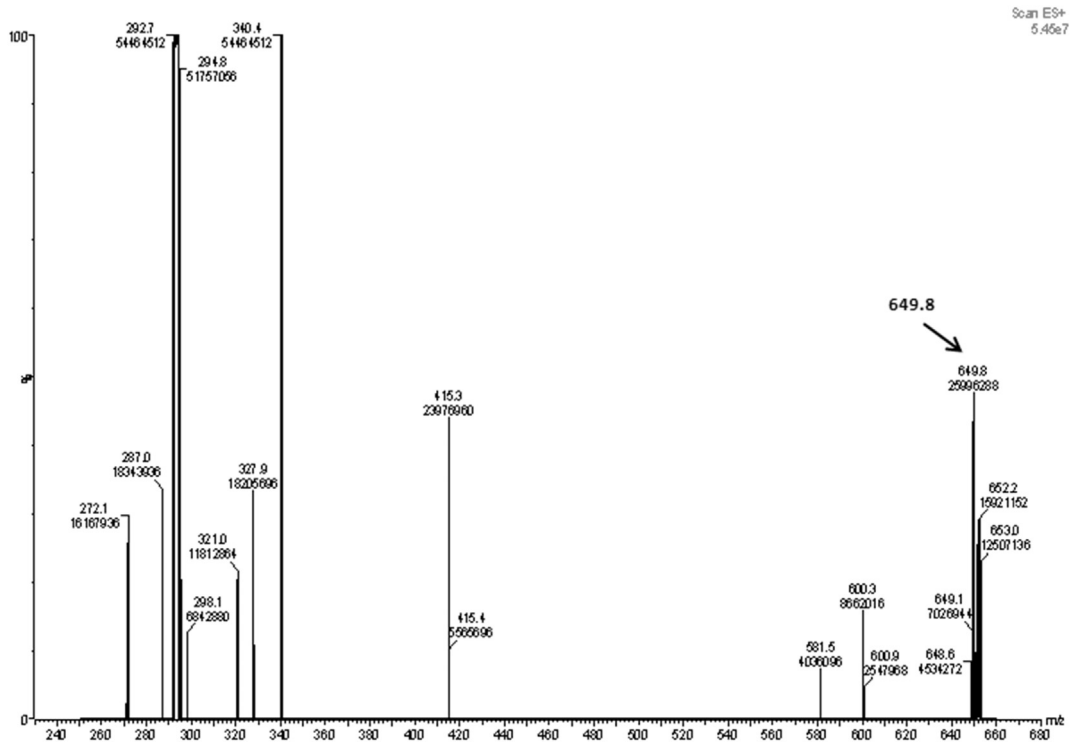


Figure 3 – Positive ion mode electrospray mass spectrum of sertraline–lactose mixture after 5 hours storage at 90°C.

In sertraline lactose mixture, the endothermic change which was related to the polymorphism was seen as a very weak peak at about 190°C. The small shift in the mixture compared to the pure sample can be due to the presence of another component in the mixture. Disappearance of sertraline melting peak and also appearance of a new endothermic peak at 215.7°C in the sertraline–lactose mixture can only indicate the interaction between the binary mixtures components under nonisothermal DSC conditions (Figure 1A).

According to Figure 1B, while increasing heating rates, DSC curves were shifted to higher temperatures. It has been previously shown that the heating rate changes have remarkable effects on the temperature range and the shape of curves [21].

3.2. FTIR

The application of FTIR is based on the integral analysis of the spectra. Study of any changes in the position or intensity of the peaks, as well as appearance or disappearance of the absorption band(s) can indicate drug instability and provide valuable information about the mechanism of the possible interaction [22,23].

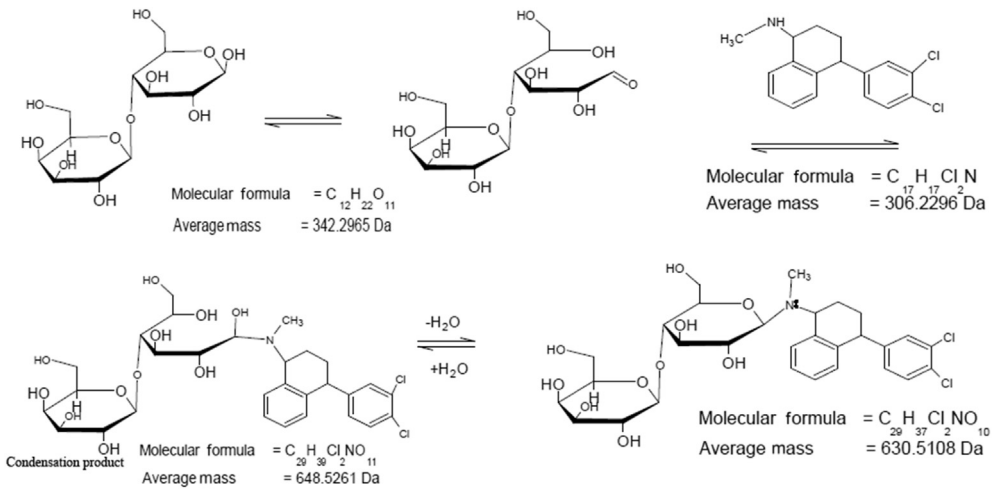
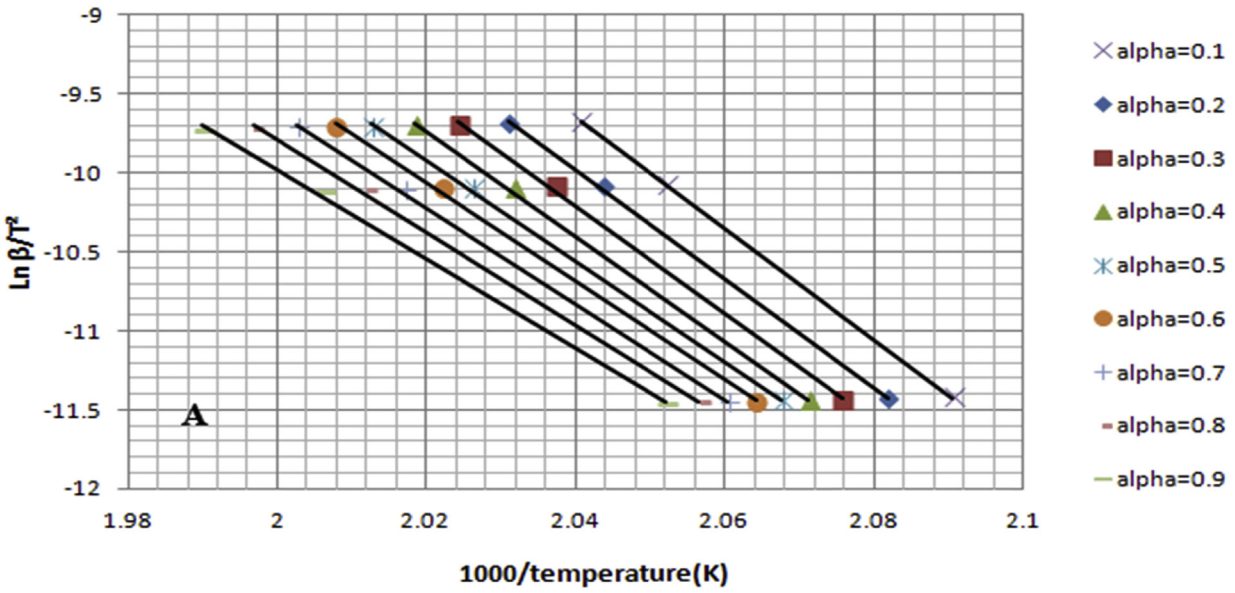
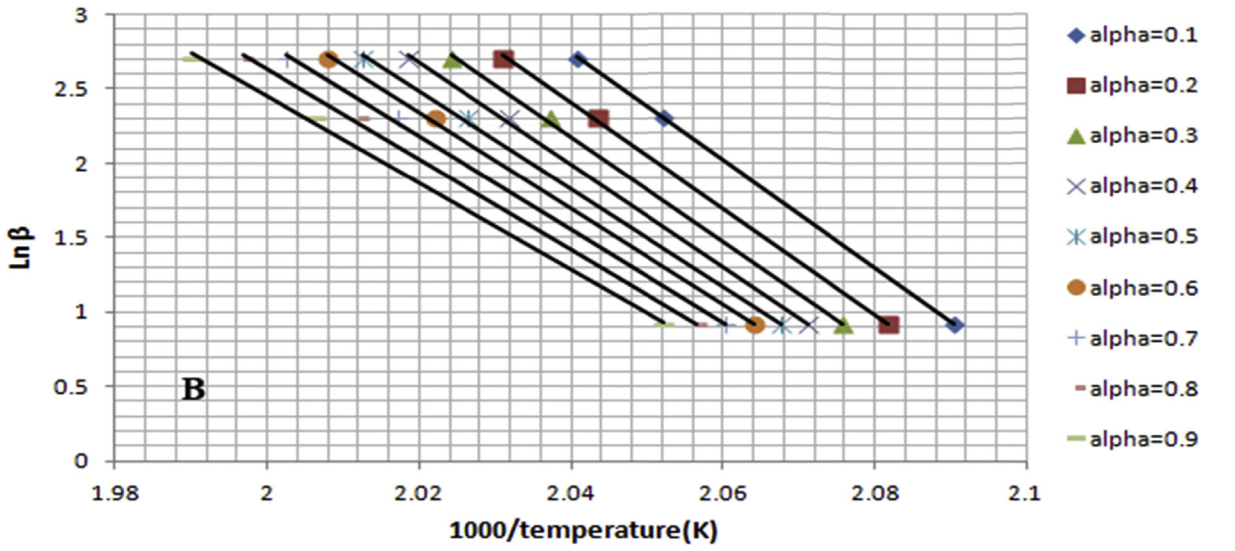
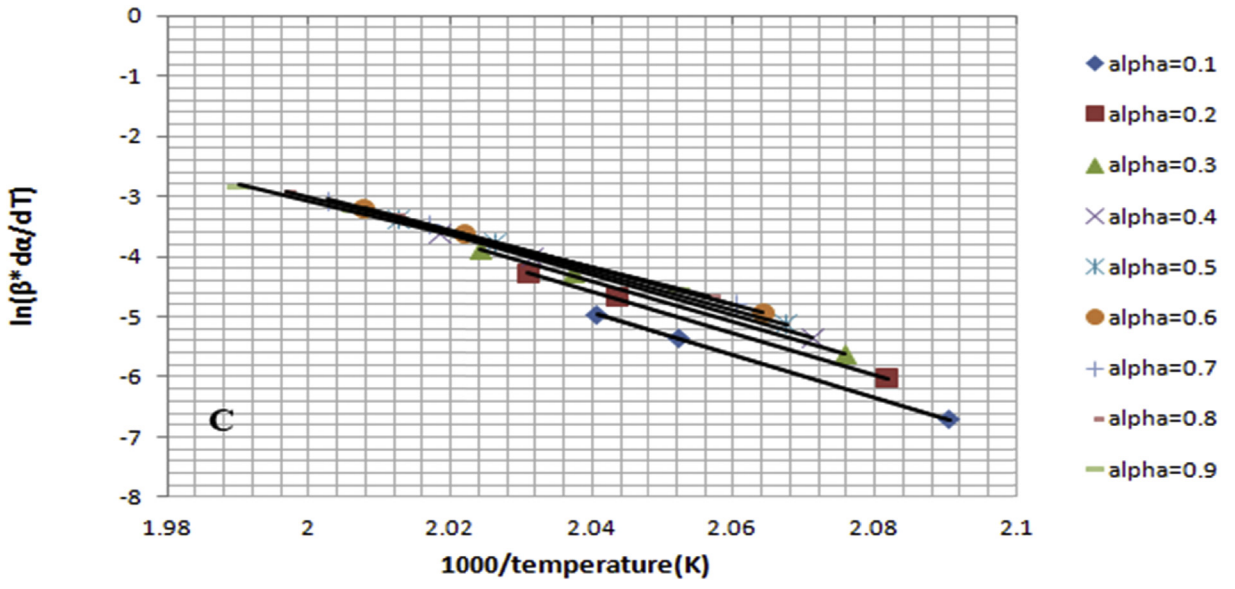


Figure 4 – Proposed structures for Maillard reaction of sertraline with lactose.

Please cite this article in press as: Ghaderi F, et al., Physicochemical analysis and nonisothermal kinetic study of sertraline–lactose binary mixtures, Journal of Food and Drug Analysis (2016), http://dx.doi.org/10.1016/j.jfda.2016.08.003







Please cite this article in press as: Ghaderi F, et al., Physicochemical analysis and nonisothermal kinetic study of sertraline–lactose binary mixtures, Journal of Food and Drug Analysis (2016), http://dx.doi.org/10.1016/j.jfda.2016.08.003

IR spectra of sertraline, lactose, and sertraline–lactose mixture immediately after mixing and 3 weeks after incubation in an oven (t = 70°C) are shown in Figure 2.

The main IR absorptions of sertraline were seen at 3420 cm^{-1} for N–H stretching, 2472 cm^{-1} for NH_2^+ vibration (due to hydrochloride salt), 1647 cm^{-1} and 1463 cm^{-1} for C–C ring vibrations, 1591 cm^{-1} for N–H bending stretching, 2934 cm^{-1} and 1399 cm^{-1} for -CH_3 vibrations, 1128 cm^{-1} for C–N stretching, 821 cm^{-1}, 776 cm^{-1}, and 738 cm^{-1} for C–Cl [24].

The main IR signals of lactose were: approximately 3459 cm^{-1}, 3292 cm^{-1}, and 2811 cm^{-1} (OH), and 2879 cm^{-1} (CH_2, CH_3).

Lactose-sertraline mixture's spectrum corresponded to the sum of each component's peaks. In the lactose-sertraline mixture after 3 weeks incubation at 70°C, new peaks with different shapes were generated at 1649 cm^{-1}, which can be related to the formation of a C=N covalent band. Also, sertraline's amine peak (1591 cm^{-1}) was eliminated, which can be indicative of the contribution of the amine functional group in the interaction and may be indicative to the Maillard reaction.

3.3. Mass spectrometry

A physical mixture of sertraline and lactose (1:1) was dissolved in a solution of NaOH 0.25M and stored at 90°C. After 5 hours, suitable dilutions were made using methanol. The diluted sample (10 μg/mL based on sertraline) was injected directly to the mass system. Mass spectra are presented in Figure 3.

The full-scan positive ion electrospray product ion mass spectra showed that the molecular ion of sertraline and the daughter ion were the protonated molecules $[M+H]^+$ of *m/z* 307.0 and 277.3, respectively [24]. Proposed structures for Maillard type interaction products are presented in Figure 4. The *m/z* value at 649.8 is related to $[M+H]^+$ of the condensation product in Figure 4.

Mass spectrometry is an appropriate and sensitive technique that is applied to a wide range of pharmaceutical compounds [25,26]. Several studies have detected the lactose and various drug substances condensation products such as hydrochlorothiazide, fluoxetine, and metoclopramide by mass spectrometry [27–29]. We have previously studied the compatibility of acyclovir, baclofen, and gabapentin with lactose in physical mixtures and commercial tablets using mass spectrometry [30–33]. According to mass results in this study, the condensation product of sertraline with lactose was successfully detected.

3.4. Kinetic study

Thermokinetic parameters were calculated based on the multiple scan method at different heating rates as a fast method for assessment of pharmaceutical products stability [21].

FR, KAS, and FWO methods have been widely applied to study the kinetic parameters in solid state interactions [11,12]. Eq. (1) corresponds to the KAS method:

$$\ln\left(\frac{\beta}{T^2}\right) = \ln\frac{A\cdot R}{E\cdot g(\alpha)} - \frac{E}{R\cdot T} \quad (1)$$

in which, T is the temperature, β is the heating rate (°C/min), g (α) is the reaction model, E is the activation energy, A is the pre-exponential factor, and R is the gas constant.

The values of ($\ln\beta/T^2$) were plotted versus 1/T and are shown in Figure 5A. Activation energy (E) was obtained from the slope of the regression straight lines and listed in Table 1.

FWO's isoconversional method is based on Eq. (2):

$$\ln\beta = \frac{\ln(A\cdot E)}{R\cdot g(\alpha)} - 5.331 - 1.052\cdot\frac{E}{R\cdot T} \quad (2)$$

The plot of lnβ versus (1/T) is shown in Figure 5B. According to the diagram, the correlation is linear. Activation energy (E) was obtained from the slopes of the straight lines and is listed in Table 1.

The isoconversional FR method is based on Eq. (3):

$$ln\left(\beta\frac{d\alpha}{dT}\right) = ln[A\cdot g(\alpha)] - \left(\frac{E}{R\cdot T}\right) \quad (3)$$

The plot of $\ln(\beta\cdot\frac{d\alpha}{dT})$ versus (1/T) is linear. The values of activation energy (E) were obtained from the slopes of the straight lines in Figure 5C for sertraline–lactose and presented in Table 1.

In Eq. (3), α is the extent of conversion.

As presented in Table 1, the values obtained by three methods are in a good agreement. Small standard deviation values showed the acceptable reproducibility of results. The reaction kinetics present important information about the reaction features and are used to compare different reaction conditions.

In all mentioned thermal models, it is assumed that reaction progresses according to the first order reaction equation [34]. Based on this assumption, the values of k, $t_{1/2}$, $t_{90\%}$, and r^2 were calculated for different heating rates. The higher the heating rate, the lower the half-life values. The maximum and minimum t1/2 values that were related to the 2.5°C/min and 15°C/min heating rates were calculated as about 75 seconds and 20 seconds, respectively. The corresponding $t_{90\%}$ was assigned as about 11 seconds and 3 seconds, respectively.

Although DSC presents a fast and versatile kinetic evaluation, the resulting data should be interpreted carefully. For example, in some cases the melting endotherm of the drug and excipient may overlay and/or the drug may be dissolved in the melted excipient which melts below the drug substance melting point. In these cases, DSC data cannot be used to evaluate the instability of the drug substance [34,35].

Figure 5 – (A) Kissinger–Akahira–Sunose diagram for sertraline and lactose at different heating rates (2.5°C/min, 10°C/min, and 15°C/min) and various conversion degrees (α = 0.1–0.9). (B) Flynn–Wall–Ozawa (FWO) diagram for sertraline and lactose at different heating rates (2.5°C/min, 10°C/min, and 15°C/min) and various conversion degrees (α = 0.1–0.9). (C) Friedman's plot for sertraline–lactose at different heating rates (2.5, 10, and 15) and various conversion degrees (α = 0.1–0.9).

Please cite this article in press as: Ghaderi F, et al., Physicochemical analysis and nonisothermal kinetic study of sertraline–lactose binary mixtures, Journal of Food and Drug Analysis (2016), http://dx.doi.org/10.1016/j.jfda.2016.08.003

Table 1 – Values for the activation energy of sertraline and lactose obtained by the Friedman (FR), Flynn–Wall–Ozawa (FWO), and Kissinger–Akahira–Sunose (KAS) methods.

Method	E, (kJ/mol), for conversion degree, α									Main value
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	
FR	290.59 ± 0.06	285.17 ± 1.54	279.88 ± 3.88	272.40 ± 4.07	259.39 ± 6.65	249.95 ± 10.95	259.41 ± 12.27	235.82 ± 9.06	228.33 ± 6.84	262.33 ± 3.42
FWO	299.83 ± 0.05	294.40 ± 1.54	289.10 ± 3.88	281.61 ± 4.07	268.60 ± 6.64	255.08 ± 16.71	268.61 ± 12.27	240.93 ± 14.84	237.52 ± 6.84	270.63 ± 4.70
KAS	291.79 ± 0.05	286.33 ± 1.53	281.00 ± 3.87	273.49 ± 4.06	260.46 ± 6.63	251.01 ± 10.94	260.45 ± 12.30	236.83 ± 9.05	229.31 ± 6.83	263.41 ± 3.41

4. Conclusion

Compatibility studies, kinetic evaluation, and tracking of the reaction product were performed using different analytical methods including DSC, FTIR, and mass spectrometry. According to DSC and FTIR results, presence of incompatibility between sertraline and lactose was revealed.

Activation energy of the proposed reaction was estimated using DSC data at different heating rates and Maillard reaction product was successfully tracked using mass spectrometry. According to the results, DSC provides fast and sensitive kinetic data, in comparison with the high performance liquid chromatography based method. In addition, mass results supported the sertraline–lactose condensation product formation as a complementary method. There is some safety information in the available literature about the Maillard reaction condensation products, which may be genotoxic, carcinogenic, or cytotoxic [33,36–38], and it would be valuable to collect toxicological data of the products in future cell based studies.

Conflicts of interest

The authors have no conflicts of interest.

Acknowledgments

This work is a part of a thesis for the award of PhD degree (No. 91) by Faranak Ghaderi, and is financialy supported by the faculty of Pharmacy, Tabriz University of Medical Sciences.

REFERENCES

[1] Narang AS, Desai D, Badawy S. Impact of excipient interactions on solid dosage form stability. Pharm Res 2012;29:2660–83.
[2] Weerawatanakorn M, Wu J-C, Pan M-H, Ho C-T. Reactivity and stability of selected flavor compounds. J Food Drug Anal 2015;23:176–90.
[3] Giron D. Applications of thermal analysis and coupled techniques in pharmaceutical industry. J Therm Anal Calorim 2002;68:335–57.
[4] Monajjemzadeh F, Farjami A. Common problems in stress testing of pharmaceutical preparations. J Mol Pharm Org Process Res 2014;3:e118.
[5] Giron D. Applications of thermal analysis in the pharmaceutical industry. J Pharm Biomed Anal 1986;4:755–70.
[6] Hasanzadeh D, Ghaffari S, Monajjemzadeh F, Al-Hallak M-K, Soltani G, Azarmi S. Thermal treating of acrylic matrices as a tool for controlling drug release. Chem Pharm Bull 2009;57:1356–62.
[7] Mojumdar S, Sain M, Prasad R, Sun L, Venart JE. Selected thermoanalytical methods and their applications from medicine to construction. J Therm Anal Calorim 2007;90:653–62.
[8] Gill P, Moghadam TT, Ranjbar B. Differential scanning calorimetry techniques: applications in biology and nanoscience. J Biomol Tech 2010;21:167.

Please cite this article in press as: Ghaderi F, et al., Physicochemical analysis and nonisothermal kinetic study of sertraline–lactose binary mixtures, Journal of Food and Drug Analysis (2016), http://dx.doi.org/10.1016/j.jfda.2016.08.003

[9] Tita B, Fulias A, Stefanescu M, Marian E, Tita D. Kinetic study of decomposition of ibuprofen under isothermal conditions. Methods 2011;15:29–32.
[10] Lotfipour F, Valizadeh H, Shademan S, Monajjemzadeh F. Efficacy and physicochemical evaluation of an optimized semisolid formulation of povidone iodine proposed by extreme vertices statistical design; a practical approach. Iranian J Pharm Res 2015;14:1015.
[11] Vyazovkin S, Dollimore D. Linear and nonlinear procedures in isoconversional computations of the activation energy of nonisothermal reactions in solids. J Chem Inf Comput Sci 1996;36:42–5.
[12] He G, Riedl B, Aït-Kadi A. Model-free kinetics: Curing behavior of phenol formaldehyde resins by differential scanning calorimetry. J Appl Polym Sci 2003;87:433–40.
[13] Verma RK, Garg S. Selection of excipients for extended release formulations of glipizide through drug–excipient compatibility testing. J Pharm Biomed Anal 2005;38:633–44.
[14] Serebruany VL, Glassman AH, Malinin AI, Nemeroff CB, Musselman DL, van Zyl LT, Finkel MS, Krishnan KR, Gaffney M, Harrison W, Califf RM, O'Connor CM. Sertraline AntiDepressant Heart Attack Randomized Trial Study Group. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. Circulation 2003;108:939–44.
[15] Bharate SS, Bharate SB, Bajaj AN. Incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review. J Excip Food Chem 2010;1:3–26.
[16] Serajuddin A, Thakur AB, Ghoshal RN, Fakes MG, Ranadive SA, Morris KR, Varia SA. Selection of solid dosage form composition through drug–excipient compatibility testing. J Pharm Sci 1999;88:696–704.
[17] Pani N, Nath L, Acharya S. Compatibility studies of nateglinide with excipients in immediate release tablets. Acta Pharm 2011;61:237–47.
[18] Huang Y, Cheng Y, Alexander K, Dollimore D. The thermal analysis study of the drug captopril. Thermochim Acta 2001;367:43–58.
[19] Ghaderi F, Nemati M, Siahi-Shadbad MR, Valizadeh H, Monajjemzadeh F. DSC kinetic study of the incompatibility of doxepin with dextrose. J Therm Anal Calorim 2015:1–10.
[20] Borochovitch R, Mendelovici M, Nidam T, Tenengauzer R, Hrakovsky J, Aronhime J. Processes for preparation of polymorphic form II of sertraline hydrochloride. Google Patents 2005. https://www.google.com/patents/US6897340.
[21] Tiţa B, Fuliaş A, Bandur G, Rusu G, Tiţa D. Thermal stability of ibuprofen. Kinetic study under non-isothermal conditions. Rev Roum Chim 2010;55:553–8.
[22] Ghaderi F, Nemati M, Siahi-Shadbad MR, Valizadeh H, Monajjemzadeh F. Physicochemical evaluation and non-isothermal kinetic study of the drug-excipient interaction between doxepin and lactose. Powder Technol 2015;286:845–55.
[23] Ghaderi F, Nemati M, Siahi-Shadbad MR, Valizadeh H, Monajjemzadeh F. Non isothermal decomposition kinetics and compatibility studies of doxepin with sucrose. Pharm Ind 2015;8:1222–8.
[24] Moffat AC, Osselton MD, Widdop B. Clarke's analysis of drugs and poisons. London: Pharmaceutical Press; 2011.
[25] Lee MS, Kerns EH. LC/MS applications in drug development. Mass Spect Rev 1999;18:187–279.
[26] Tsai C-F, Kuo C-H, Shih DY-C. Determination of 20 synthetic dyes in chili powders and syrup-preserved fruits by liquid chromatography/tandem mass spectrometry. J Food Drug Anal 2015;23:453–62.
[27] Harmon PA, Yin W, Bowen WE, Tyrrell R, Reed RA. Liquid chromatography–mass spectrometry and proton nuclear magnetic resonance characterization of trace level condensation products formed between lactose and the amine-containing diuretic hydrochlorothiazide. J Pharm Sci 2000;89:920–9.
[28] Qiu Z, Stowell JG, Morris KR, Byrn SR, Pinal R. Kinetic study of the Maillard reaction between metoclopramide hydrochloride and lactose. Int J Pharm 2005;303:20–30.
[29] Wirth DD, Baertschi SW, Johnson RA, Maple SR, Miller MS, Hallenbeck DK, Gregg SM. Maillard reaction of lactose and fluoxetine hydrochloride, a secondary amine. J Pharm Sci 1998;87:31–9.
[30] Monajjemzadeh F, Hassanzadeh D, Valizadeh H, Siahi-Shadbad MR, Mojarrad JS, Robertson T, Roberts MS. Assessment of feasibility of Maillard reaction between baclofen and lactose by liquid chromatography and tandem mass spectrometry, application to pre formulation studies. AAPS PharmSciTech 2009;10:649–59.
[31] Monajjemzadeh F. LC-mass as a complementary method in detecting drug-excipient incompatibility in pharmaceutical products. J Mol Pharm Org Process Res 2014;2:e110.
[32] Monajjemzadeh F, Hassanzadeh D, Valizadeh H, Siahi-Shadbad MR, Mojarrad JS, Robertson TA, Roberts MS. Detection of gabapentin-lactose Maillard reaction product (Schiff's Base): application to solid dosage form preformulation. Part 1. Pharm Ind 2011;73:174–7.
[33] Shadbad MR, Ghaderi F, Hatami L, Monajjemzadeh F. Investigation of possible Maillard reaction between acyclovir and dextrose upon dilution prior to parenteral administration. AAPS PharmSciTech 2016;10:1–9.
[34] Qi S, Belton P, Nollenberger K, Clayden N, Reading M, Craig DQ. Characterisation and prediction of phase separation in hot-melt extruded solid dispersions: a thermal, microscopic and NMR relaxometry study. Pharm Res 2010;27:1869–83.
[35] Wissing S, Craig DQ, Barker SA, Moore WD. An investigation into the use of stepwise isothermal high sensitivity DSC as a means of detecting drug-excipient incompatibility. Int J Pharm 2000;199:141–50.
[36] Fuliaş A, Doca N, Vlase G, Tiţa B, Tiţa D, Vlase T. Thermal decomposition kinetics of cefadroxil. Rev Roum Chim 2011;56:967–73.
[37] Díaz IBZ, Chalova VI, O'Bryan CA, Crandall PG, Ricke SC. Effect of soluble maillard reaction products on cadA expression in Salmonella typhimurium. J Environ Sci Health B 2010;45:162–6.
[38] Delgado-Andrade C, Morales FJ, Seiquer I, Navarro MP. Maillard reaction products profile and intake from Spanish typical dishes. Food Res Int 2010;43:1304–11.

Please cite this article in press as: Ghaderi F, et al., Physicochemical analysis and nonisothermal kinetic study of sertraline–lactose binary mixtures, Journal of Food and Drug Analysis (2016), http://dx.doi.org/10.1016/j.jfda.2016.08.003