

Tracking of the Maillard reaction products in Pharmaceutical formulations of sertraline hydrochloride

Faranak Ghaderi¹, Mahboob Nemati^{2,3,4}, Mohammad R. Siahi-Shadbad^{2,4}, Hadi Valizadeh⁵, Farnaz Monajjemzadeh^{2,3*}

¹ Department of Pharmaceutical and Food Control, School of pharmacy, Urmia University of Medical Sciences, Urmia, Iran

² Department of Pharmaceutical and Food Control, Faculty of pharmacy Tabriz, University of Medical Sciences, Tabriz, Iran

³ Food and drug safety research center, Tabriz University of Medical Sciences, Tabriz, Iran

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

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

Corresponding author: Farnaz Monajjemzadeh, Department of Pharmaceutical and Food Control, Tabriz University of Medical Sciences

E-mail: Monaggemzadeh@tbzmed.ac.ir, Monajjemzadehf@yahoo.com

Zip code: 5166414766, Tel: +9841133392606

Abstract

In the present paper the physicochemical incompatibility of sertraline with dextrose was evaluated in oral liquid formulations. Different physicochemical methods such as differential scanning calorimetry (DSC), Fourier-transform infrared (FTIR) spectroscopy and mass spectrometry were applied to assess sertraline - dextrose incompatibility. Non-Isothermally stressed physical mixtures were used to study the solid-state kinetic parameters. Different thermal models such as Friedman, Flynn-Wall-Ozawa (FWO) and Kissinger-Akahira-Sunose (KAS) were used to calculate the activation energy of drug-excipient interaction.

The aim of this study was to evaluate the kinetic parameters using a fast and sensitive DSC method.

Overall, the incompatibility of sertraline as an amine containing drug with dextrose as a reducing carbohydrate was successfully evaluated. DSC based kinetic analysis can provide rapid and easy evaluation of different drug-excipient mixtures incompatibilities. Special considerations should be made regarding the Maillard incompatibility reaction in the formulation design of liquid formulations containing dextrose or natural herbal extracts as sweeteners.

Keywords: Sertraline, Dextrose, Incompatibility, Kinetic, DSC, Mass

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Introduction

“Reducing sugars may react with active ingredients in pharmaceutical dosage forms.

Dextrose is a well-known reducing carbohydrate that is widely used in pharmaceutical manufacturing. The main roles of dextrose in pharmaceutical formulations are as a sweetener in solid and liquid oral formulations, wet granulation diluent and binder in solid formulations, and as a direct-compression tablet diluents in chewable tablets (1).

Pharmaceutical oral solutions may contain one or more active ingredients in an appropriate solvent and may contain sweetening agents, suitable antimicrobial agent, antioxidants, flavoring and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilizing, stabilizing and coloring agent. Sweetening agents and flavors are generally used in oral formulations to cover drug bitterness and to make the formulation more acceptable (2). Sucrose is the most common sweetener and flavor used in oral pharmaceutical solutions (1). The hydrolysis of sucrose

can be induced simply by heating an aqueous solution. Thus in the manufacturing process of syrup formulations, heating may cause sucrose convert to dextrose and fructose. It is interesting to note that, the sugar/sugars in fruit juices such as grape juice and other juices, (which are used in so called sugar-free syrups) are mainly composed of dextrose and fructose (3).

Dextrose as a reducing sugar can participate in the Maillard reaction with amine containing drugs such as sertraline (4, 5).

Sertraline ((1*S*, 4*S*)-4-(3, 4-dichlorophenyl)-*N*-methyl-1, 2, 3, 4-tetrahydronaphthalen-1-amine) is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) group. This drug prescribed for major depression, panic, obsessive-compulsive disorder, social anxiety, and premenstrual dysphoric disorders (PMDD) (6).

According to the best of our information, although there are some relevant studies in food science, no attention has been paid to the feasibility of the Maillard reaction in oral liquid pharmaceutical formulations (7, 8). In 2002 Sara I.F. SMartins et.al reviewed maillard reaction in food and the kinetic of this reaction (9). M.A.J.S.van Boekel in a research discussed about the importance of maillard reaction in food quality and flavor compound generation (10). In this study the stability problems of sertraline and dextrose was evaluated using DSC and FTIR. Also the activation energy of this interaction was calculated by fast and sensitive DSC multiple scan method at different heating rates and the Maillard reaction product was tracking using mass spectrometry.

Materials and Methods

Sertraline was obtained from Novin Kavosh Mamatir Co. (Tehran, Iran). Dextrose and NaOH was provided from Merck, (Darmstadt, Germany). All other reagents were of analytical grade and were provided from Merck, (Darmstadt, Germany).

DSC (Differential Scanning Calorimetry):

Shimadzu differential scanning calorimeter (Kyoto, Japan) was used for thermal analysis of drug-excipient physical mixture. Binary mixture (10 g) prepared by weighing equal masses of sertraline and dextrose and uniform mixing into an amber glass flask by tumbling method. Then 5 mg of each sample was weighed in the DSC aluminium pan and scanned in the temperature range of 25–300 °C at various heating rates (2.5, 10, and 15 °C/min). Calculations were performed using TA-60 software (version 1.51).

FTIR (Fourier-transform infrared spectroscopy):

Sertraline and dextrose were mixed in 1:1 mass ratios and according to Serajuddin et al. method 20% (v/w) water was added to samples and stored in closed vials at 90 °C for 24 hours (11). Proper controls were done using pure drug and excipient in dry and wet conditions.

FTIR spectra were recorded immediately after mixing and also after storage using potassium bromide disc (Bomem, MB-100 series, Quebec, Canada). The spectrum was an average of ten 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).

Mass spectrometry:

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

Results

Thermal analysis is a set of methods in which a property of the tested material is studied as it changes with temperature. These techniques have been extensively used for the assessment of possible interactions between formulation components of pharmaceutical dosage forms since 1970 and give

valuable data about API (active pharmaceutical ingredient) - excipients incompatibility which might lead to significant changes in the chemical properties, stability, solubility, absorption and therapeutic response of drugs (12, 13).

Application of differential scanning calorimetry (DSC) is extensively applied in pharmaceutical industries as a rapid method to evaluate the physical properties of drug substances and compatibility studies of formulation components (14-16).

Multiple scan method at different heating rates using isoconversional calculation procedures is an alternative to the conventional time consuming method, in order to calculate solid-state kinetic parameters. Friedman (FR) Kissinger–Akahira–Sunose (KAS) and Flynn–Wall–Ozawa (FWO) methods have been widely used to study the kinetic parameters (17-19).

DSC commonly used in the pharmaceutical science and provides valuable data such as, formulation component compatibility, drug purity, drug stability, polymorphic forms and their stabilities (20-23).

DSC (Differential Scanning Calorimetry):

Selected DSC curves of sertraline, dextrose and sertraline – dextrose mixtures are shown in Fig.1

And were used to thermal analysis of mentioned samples.

According to Fig.1A, 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 (24).

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

Disappearance of sertraline melting peak and also appearance of new endothermic peak at 172°.°C in sertraline-dextrose mixture can only indicate the interaction between the mixtures components (Fig.1A).

As can be seen in the Fig.1B, while increasing heating rates, DSC curves were shifted to higher temperatures. It has been previously resulted that the heating rate changes have significant Effects on the temperature range and the shape of curves (25).

FTIR (Fourier-transform infrared spectroscopy):

FTIR spectrometer can provide valuable information about the mechanism of this interaction based on study of any changes in the position or the intensity of the peaks, as well as appearance or disappearance of the absorption band.

IR spectra of sertraline, dextrose, sertraline-dextrose mixture immediately after mixing, and 24 hours after incubation in an oven ($t=90$ °C) is shown in Fig2.

Sertraline IR's main signals appeared at ~ 3420 (N—H stretching), 2472 (NH_2^+ due to hydrochloride salt), 1647 and 1463 and (C-C ring vibration) 1591 (N-H bending stretching), 2934 cm^{-1} ($-\text{CH}_3$), and principal peaks at wave numbers 1399 (C-H, CH_3), 1128(C—N stretching), 821, 776 and 738 cm^{-1} (C—Cl)(26).

Dextrose monohydrate IR main peaks including: 3315, 2936 and 2531 ($-\text{OH}$), 2887($-\text{CHO}$), 1447($-\text{CH}_2-$).

Sertraline-Dextrose mixture's main signals were corresponding to the sum of each component's peaks. In dextrose -Sertraline mixture, a significant peak was observed at 1592 cm^{-1} .

Although sertraline had a small vibration at about 1591 cm^{-1} , this peak was very stronger than

the pure drug. This vibration can be related to the formation of a C=N covalent band. Controls were done using sertraline and dextrose pure samples. No change was observed in control samples.

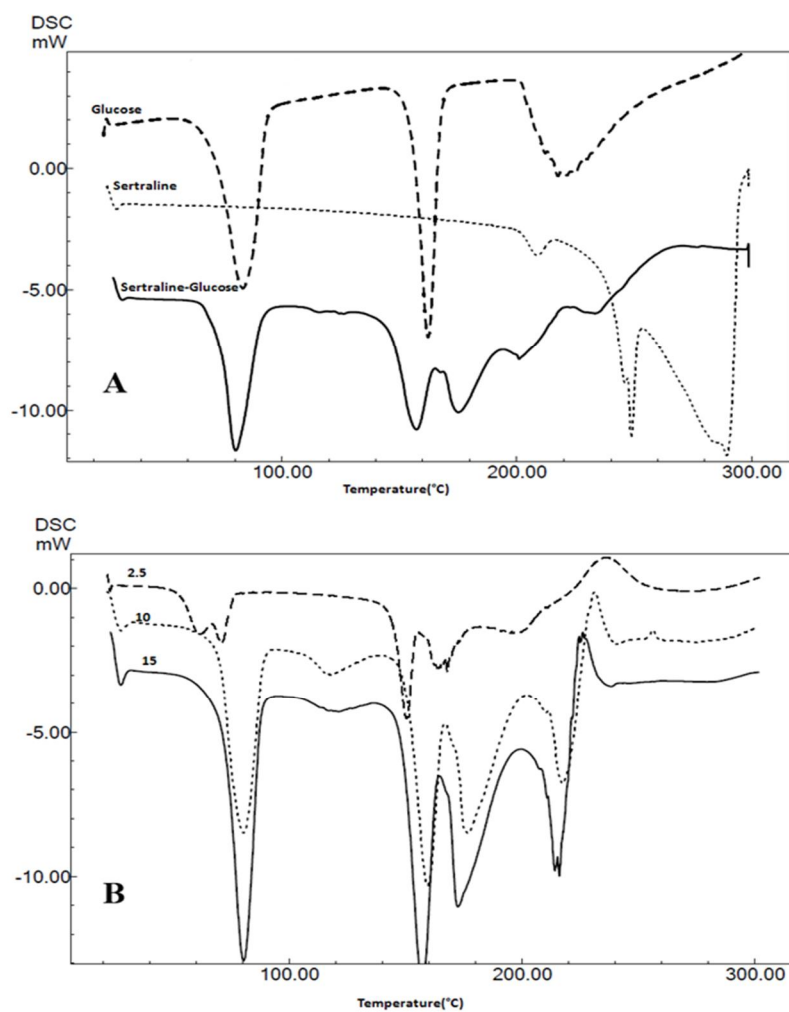


Fig 1. Selected DSC curves of (A) sertraline, dextrose and sertraline-dextrose 1:1 W/W binary mixture ($\beta=10\text{ }^{\circ}\text{C}/\text{min}$).
(B) Sertraline at different heating rates ($\beta=2.5$, $\beta=10$, $\beta=15\text{ }^{\circ}\text{C}/\text{min}$).

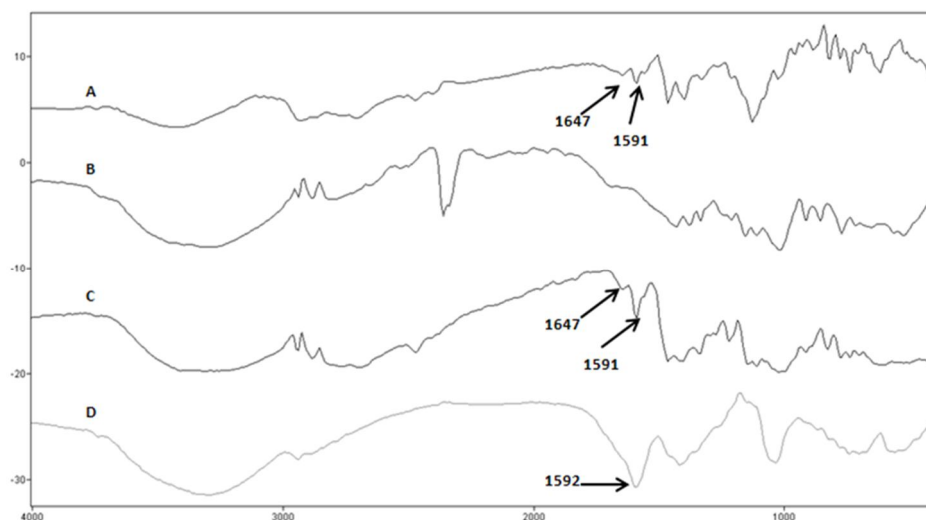


Fig 2. FTIR spectra of (A) sertraline (B) dextrose (C) sertraline -dextrose 1:1 W/W binary mixture immediately after mixing, and (D) binary mixture with 20% added water after 24 hours incubation at $90\text{ }^{\circ}\text{C}$.

Mass spectrometry:

Physical mixture of sertraline and dextrose (1:1) was dissolved in a solution of NaOH 0.25M and stored at 90 °C. After 5 hours this sample injected to the mass system. Mass spectra are presented in Fig.3.

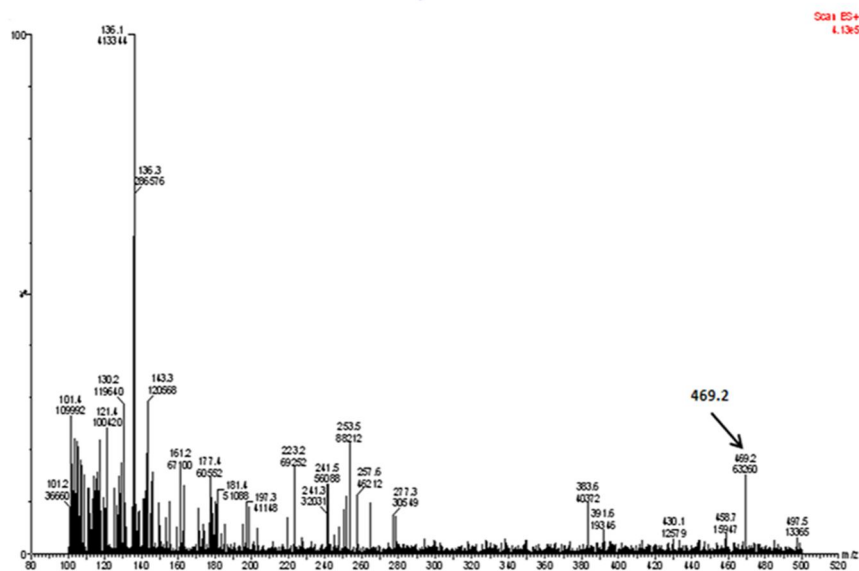


Fig 3. Positive ion mode electrospray mass spectrum of sertraline-dextrose mixture after 5 hours storage at 90 °C

The full-scan positive ion electrospray product ion mass spectra showed that the molecular ion of sertraline and daughter ion were the protonated molecules (M+H)⁺ of m/z 307.0 and 277.3 respectively (26). Suggested structures for Maillard type interaction products have been presented in Fig. 4. The m/z value at 469.2 is related to (M+H)⁺ of condensation product in Fig 4(mass resolution=2).

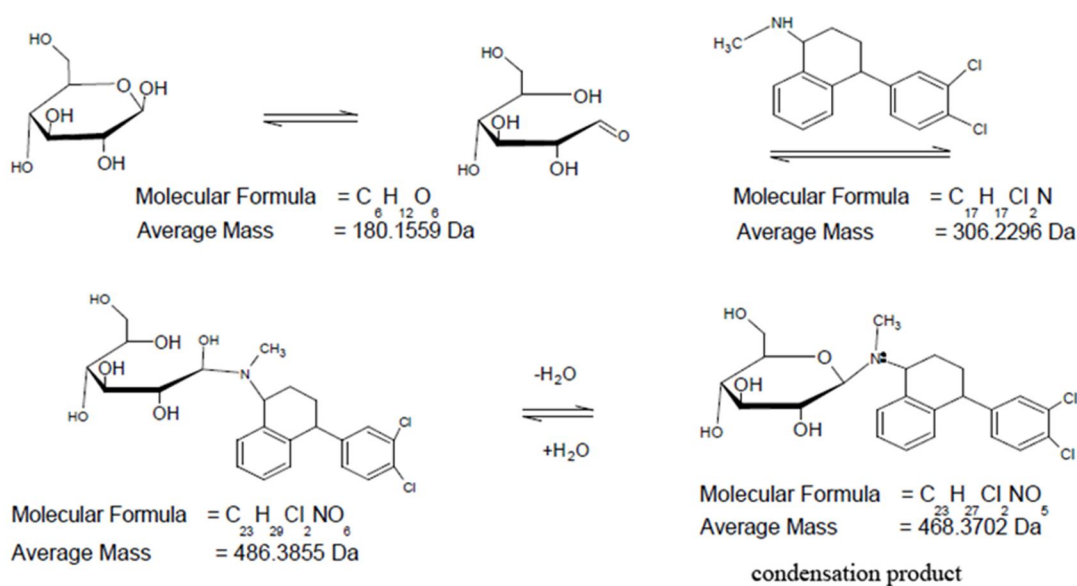


Fig 4. Suggested structures for Maillard reaction of sertraline with dextrose.

Mass spectrometry is a suitable and precise technique that is extensively used in drug development (27). A number of studies have found the lactose and various drug substances such as hydrochlorothiazide, fluoxetine and metoclopramide condensation products by mass spectrometry (28-30). We have previously evaluated the Maillard reaction product of acyclovir, baclofen and gabapentin with lactose using mass spectrometry (31, 32). However, there have been no studies about the Maillard reaction product of drug substance and dextrose. In present study the condensation product of sertraline with dextrose was successfully detected using mass spectrometry.

Kinetic study:

Multiple scan method at different heating rates using DSC has been proposed as a fast method for kinetic study (33).

Friedman (FR), Kissinger–Akahira–Sunose (KAS) and Flynn–Wall–Ozawa (FWO) methods have been recently used to kinetic analysis in solid state interactions for evaluation of pharmaceutical products.

Equations 1, 2 and 3 are corresponding to the Kissinger–Akahira–Sunose (KAS), Flynn–Wall–Ozawa (FWO) and Friedman methods respectively.

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

Equation 1

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

Equation 2

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

Equation 3

In which, T is the temperature, β is heating rate ($^{\circ}\text{C}/\text{min}$), $g(\alpha)$ is reaction model, E is activation energy, A is the pre-exponential factor, α is the extent of conversion and R is the gas constant

In KAS method the values of $(\ln\beta/T^2)$ were plotted vs. $1/T$ and activation energy (E) of sertraline- dextrose

interaction was obtained from slope of the straight lines in Fig. 5A and listed in table 1.

FWO diagram is shown in Fig.5B. According to this diagram the plot of $\ln\beta$ vs. $(1/T)$ is linear. Activation energy (E) of mentioned reaction was obtained from the slopes of the straight lines and listed in table 1.

The Friedman plot resulted of $\ln\left(\beta \cdot \frac{d\alpha}{dT}\right)$ vs. $(1/T)$. The values of activation energy (E) of the noted reaction was obtained from the slopes of the straight lines in Fig.5C and presented in table1.

The calculated mean values for the activation energy using Friedman (FR), Kissinger–Akahira–Sunose (KAS) and Flynn–Wall–Ozawa (FWO) methods were, 178, 185 and 178 kJ mol^{-1} respectively (Table 1).

As presented in tables 1 the activation energy obtained by three methods are in a good agreement. The reaction kinetic gives valuable information about the reaction features and is used to distinct various reaction conditions.

DSC presents fast and appropriate evaluation but data obtained by DSC should be interpreted more carefully.

Kinetic evaluations using DSC based methods are only done for solid samples. In pharmaceutical researches such studies provide reaction kinetic data in order to have an estimate of the reaction possibility between different pharmaceutical agents. Several studies have been performed in this issue. Fulas et al. were determined the activation energies for decomposition of cefadroxil using DSC curves. The calculated activation energies for decomposition of cefadroxil and cefadroxil-magnesium stearate interaction were 358.53 ± 1.60 and 257.99 ± 2.62 respectively (33). According to our results the mean activation energy obtained for doxepin-sucrose, doxepin–lactose and doxepin dextrose was 190.81 ± 4.67 , 288.88 ± 3.96 and 224.23 ± 5.55 (16, 19, 34).

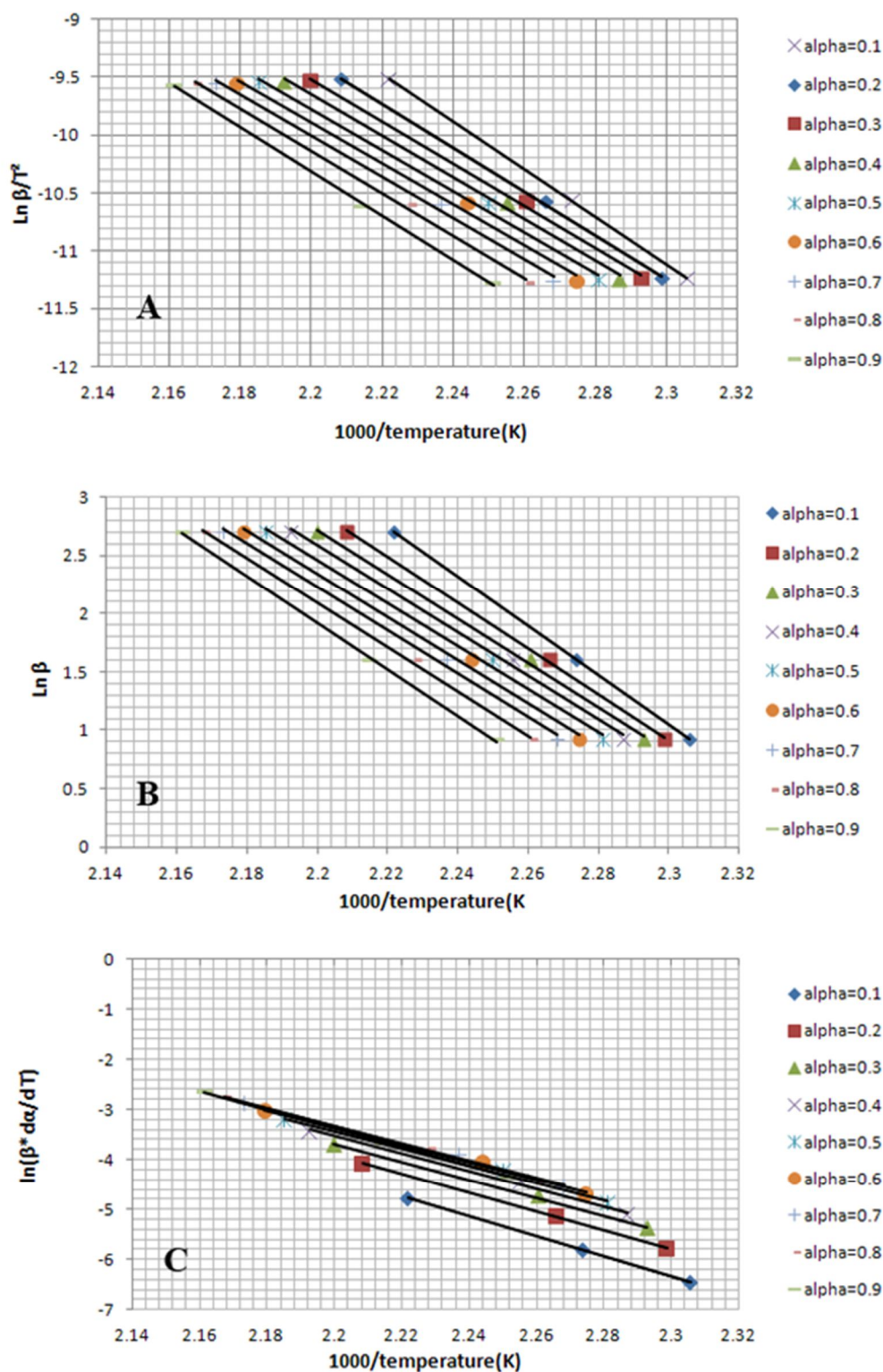


Fig 5. (A) The Kissinger–Akahira–Sunose diagrams for sertraline and dextrose (B) The Flynn–Wall–Ozawa (FWO) diagrams for sertraline and dextrose (C)Friedman's plot for for sertraline and dextrose at different heating rates (2.5,10 and 15 °C/min)and various conversion degrees ($\alpha = 0.1$ to 0.9).

Table 1. Values for the activation energy of sertraline and dextrose obtained by the Friedman, Flynn–Wall–Ozawa and Kissinger–Akahira–Sunose methods.

Method	E, (kJ mol ⁻¹), 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	199.24	200.09	195.84±	190.19	180.68	174.27±	166.48	153.56	140.92	177.92
	±5.99	±8.61	8.26	±7.34	±8.04	6.05	±6.33	±3.76	±6.19	±6.19
FWO	206.05	208.40	204.64±	196.98	187.96	180.55±	174.74	159.86	145.66	184.98
	±9.98	±10.64	9.39	±11.29	±11.27	10.67	±8.12	±8.29	±8.01	±9.72
KAS	200.39	201.22	196.95±	191.28	181.75	175.32±	167.50	154.55	141.88	178.98
	±7.62	±10.21	9.88	±8.88	±9.55	7.53	±7.78	±5.10	±2.26	±7.69

Discussion

Compatibility studies, kinetic evaluation and tracking of the reaction product were performed using different analytical methods included DSC, FTIR and mass spectrometry. According to DSC and FTIR results, presence of incompatibility between sertraline and dextrose as sweetener in oral liquid formulations was successfully evaluated.

Activation energy of the proposed reaction was estimated using DSC data at different heating rates and Mass results supported the sertraline-dextrose condensation product of the Maillard reaction. Several studies have argued about the genotoxic, carcinogenic, or cytotoxic effects of the Maillard's reaction products (35). Thus special considerations should be made regarding the Maillard incompatibility reaction in the formulation design of liquid formulations containing dextrose or natural herbal extracts as sweeteners. More studies such as NMR can be used as complementary methods to prove the identity of the product/products formed due to sertraline-dextrose Maillard reaction. To this purpose a preparative experiment should be established to provide an almost pure solid mass of the product/products.

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Conflict of interest

The authors declare no financial or other conflict of interest.

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