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Original Article

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

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ARTICLE INFO

*Article history:*
Received 25 July 2015
Received in revised form
22 June 2016
Accepted 21 August 2016
Available online 3 November 2016

*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

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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

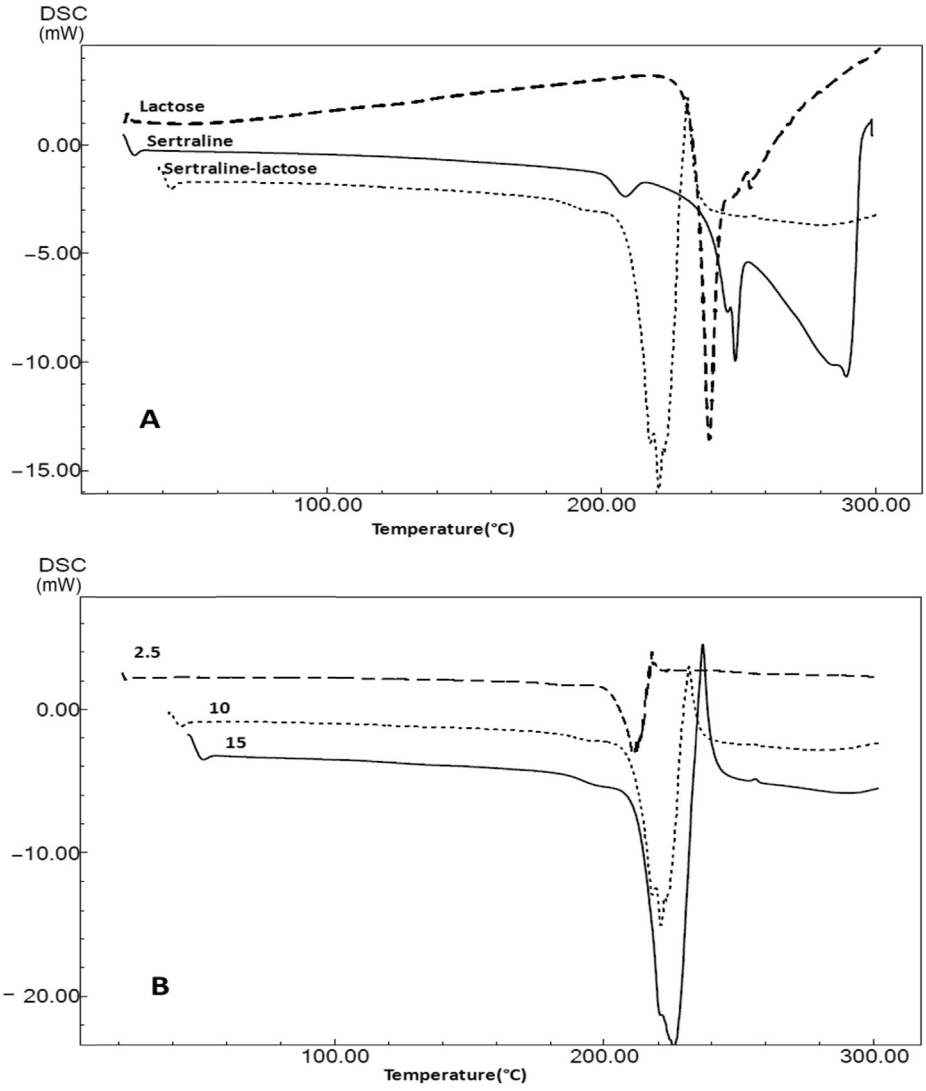


**Figure 1 – Selected differential scanning calorimetry (DSC) curves of (A) sertraline, lactose, and sertraline–lactose mixture with 1:1 mass ratio (β = 10) and (B) sertraline lactose 1:1 w/w binary mixture at different heating rates (β = 2.5, β = 10, β = 15).**