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Physicochemical evaluation and non-isothermal kinetic study of the drug–excipient interaction between doxepin and lactose

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ABSTRACT

In this study, the incompatibility of doxepin in solid physical mixtures with lactose (monohydrate and anhydrous) was investigated. The compatibility testing was made using various physicochemical techniques, such as differential scanning calorimetry (DSC), Fourier-transform infrared (FTIR) spectroscopy, and mass spectrometry. Non-isothermally stressed physical mixtures were used to analyze the solid-state kinetic parameters. Data were fitted to different thermal models, such as Friedman, Flynn–Wall–Ozawa (FWO) and Kissinger–Akahira–Sunose (KAS) for different drug–excipient mixtures separately. Overall, the incompatibility of doxepin as a tertiary amine, with lactose as a reducing carbohydrate was successfully evaluated. DSC based kinetic analysis provided a simple and fast comparative data in different drug–excipient mixtures. It can be recommended to exclude lactose from doxepin's solid dosage formulations, and also to use the described procedure in the kinetic evaluation of drug–excipient incompatibility studies.

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1. Introduction

An assessment of the incompatibilities between the drug substance and the excipients is important during preformulation studies, and the quality control of pharmaceutical dosage forms. Drug and excipients may change their chemical and physical stability of pharmaceutical formulations, which may consequently lead to altered bioavailability, as well as the efficacy. It also increases the safety of the medicinal product [1,2]. Common drug–excipient interactions which have been reported till now are acid–base and Maillard interactions. Maillard type of reaction is defined as a probable incompatibility reactions in amine-containing drugs, such as doxepin and reducing excipients, which leads to formation of a Schiff's base as an unstable intermediate reaction product. It then undergoes Amadori rearrangement and generates a ketoamine compound [1,3]. This type of incompatibility leads to a color abrasion, and results in new chemical entities with unknown efficacy and suspected safety. From the safety issues, it is previously reported that Maillard reaction products, which are generated from aldose and ketose–lysine reactants have a cytotoxic effect on both rat and human cells [4].

Various analytical methods have been employed to prove this type of interaction, such as thermal analysis, UV and infra-red spectroscopy, mass spectrometry and NMR studies.

Doxepin, a dibenzoxepin-derivative tricyclic antidepressant is used to treat depression disorders, anxiety, insomnia, and as a second line treatment for chronic idiopathic urticaria [5,6]. This drug was first approved in 1969. Its mechanism of action is inhibition of serotonin and norepinephrine reuptake. Thus, it acts as an antagonist at various serotonergic, adrenergic, muscarinic, dopaminergic and histaminergic receptors [7]. Its chemical formula is $C_{19}H_{21}NO$, and its structure is shown in Fig. 1.

Although it has been previously shown that different amine containing drugs (primary and secondary amines), such as baclofen and acyclovir, can interact with reducing carbohydrates via the Maillard reaction, there is only one report about a type 3 amine containing drug (promethazine), with no detailed analytical evaluation which makes this hypothesis as a simple assumption [8].

Although Maillard reaction is a well-known chemical interaction, there is still a great tendency to utilize lactose for a wide range of solid dosage formulations in pharmaceutical industries worldwide. Literature has shown that there is a lack of information about the involvement of a

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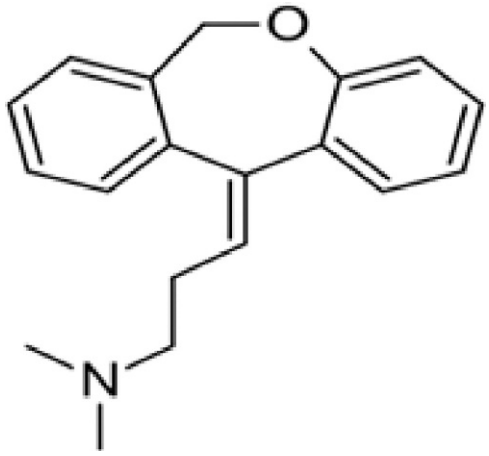

Fig. 1. Structure of doxepin.

tertiary amine drug, such as doxepin in Maillard type interaction with lactose.

Thus, in this research, the possibility of the Maillard reaction in doxepin, with only one tertiary amine moiety will be evaluated using simple and sophisticated analytical techniques. Finally, non-isothermal DSC methods will be utilized to assess the kinetic information in different drug–excipient mixtures, to be able to predict the remaining drugs in various conditions.

2. Materials and methods

2.1. Materials

Doxepin (3-(6*H*-benzo[*c*][1]benzoxepin-11-ylidene)-*N*,*N*-dimethylpropan-1-amine) was obtained from Dipharma Francis Pharmaceutical Co. (Baranzate, Italy). Monohydrate and anhydrous lactose were provided from DMV Chemical Co. (Veghal, Netherlands). Acetonitrile and formic acid were purchased from Merck (Darmstadt, Germany). All other chemicals were of HPLC grade and were obtained from Labscan Analytical Science (Dublin, Ireland). Generic preparations of doxepin named Brands 1–3 were acquired in local pharmacies in Iran.

2.2. Methods

2.2.1. DSC (differential scanning calorimetry)

A DSC-60, Shimadzu differential scanning calorimeter (Kyoto, Japan), with TA-60 software (version 1.51) was used for thermal analysis of drug and excipients alone, or in binary mixtures. Binary mixtures (10 g) were prepared from equal masses of doxepinand each excipient which were weighed individually into amber glass flasks and uniform blending was ensured by tumbling method. Then, 5 mg of each sample was weighed and compressed in the DSC aluminum pan, and pressed using a cap. Consequently, it was scanned in the temperature range of 25–300 °C, with different heating rates (2.5, 5, 7.5, 10 and 15 °C/min).

2.2.2. FTIR (Fourier-transform infrared) spectroscopy

Doxepin and excipients were blended in 1:1 mass ratios. They were mixed with 20% (v/w) water and were stored in closed vials at 70 °C for 24 hours [9].

FTIR spectra were obtained immediately after mixing and also after incubation at elevated temperatures at predetermined time intervals, using potassium bromide disc preparation method (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 were processed by GRAMS/32 version 3.04 (Galactic Industries Corporation, Salem, NH).

2.2.3. Mass spectrometry

Mass analysis was performed on the Waters 2695 (Milford, Massachusetts, USA) Quadrupole Mass system, at electron-spray ionization mode, with positive ionization, capillary voltage of 3.5 V, cone voltage of 30 V, extractor voltage of 3 V, RF lens voltage of 0.50 V, source temperature (80 °C) desolvation temperature (200 °C), desolvation gas flow (310 L/h) and cone gas flow (60 L/h).

2.2.4. TLC

TLC method was as described in our previous study [10]. A mixture of ethyl acetate and methanol (1:3 v/v) containing 0.25% v/v glacial acetic acid was used as the mobile phase. Lactose with a concentration of (1 mg/mL) in diluent solution (methanol:water (2:3 v/v)), was spotted as the reference standard. Twenty units of each brand tablets (brands 2 and 3) or capsules (brand 1) were weighed and the mean weight was calculated. Assuming that the entire excipient content of the average weight is lactose, an equivalent of 25 mg lactose in powdered tablets and capsules content was transferred to a 25-mL volumetric flask and was diluted to 1 mg/mL. Standard and test solutions (2 μL) were spotted on a thin-layer chromatographic plate individually (2020, Silica gel-60 F254, 0.25 mm thickness prepared from Merck [Darmstadt, Germany]).

The spots were dried and placed in a separation chamber, which was previously saturated with the solvent. The plate was removed from the chamber before the solvent front reached the top of the stationary phase. It was dried with a stream of hot air, sprayed uniformly with staining solution containing 0.5 g thymol in 95 mL alcohol and 5 mL sulfuric acid. Later, the plate was heated at 130 °C for 5 min. As shown in Fig. 2, the presence of lactose was approved when the main spot resulted from these brands was similar to the standard solution in appearance and R_f (Retention Factor) values. Lactose was present in one domestic brand, and also in a foreign innovator brand.

2.3. Kinetic study

Comparative thermal stability of doxepin and lactose (monohydrate and anhydrous) mixtures was determined using the kinetic parameters in non-isothermal condition. Calculations were made on the resultant DSC curves, using differential models, such as the Friedman method [11,12] and also integral modes, such as Kissinger–Akahira–Sunrose (KAS) and Flynn–Wall–Ozawa (FWO) methods [13].

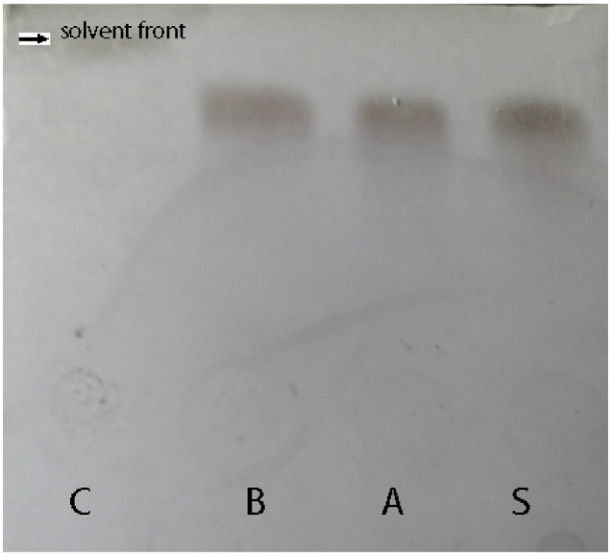

Fig. 2. TLC results of (S) lactose, (A) Brand 1, (B) Brand 2 (innovator), and (C) Brand 3.

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