



Evaluation of Celecoxib-Lactose Incompatibility Reactions at Solid State using Physicochemical Methods

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Abstract

Background & Aims: Drug excipient incompatibility evaluation is an important part of pre-formulation studies. Drug-excipient interaction may affect drug stability, bioavailability, therapeutic effects, efficacy, and safety. Therefore, development of a successful drug delivery systems or dosage forms depends on correct selection of excipients. The aim of this study is to evaluate of celecoxib-lactose incompatibility reactions at solid state using physicochemical methods.

Materials & Methods: Celecoxib and lactose were blended in 1:1 mass ratios and added to 20% (v/w) water and stored in closed vials at 60°C (inside the oven). Also, pure drug and pure excipient were prepared. Celecoxib, celecoxib-lactose and lactose tablets prepared using direct compression method. Produced tablets were stored at 60 °C (inside the oven). Finally, celecoxib -lactose incompatibility in the solid state was investigated by Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) methods over four consecutive weeks.

Results: the incompatibility of celecoxib with lactose was not observed using physicochemical methods including DSC, FTIR spectroscopy and also visual observation.

Conclusion: It can be concluded that using lactose in celecoxib solid pharmaceutical preparations will not cause incompatibilities.

Keywords: Incompatibility, Excipient, Celecoxib, Lactose

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Introduction

The study of the interaction between drugs and excipients is one of the most vital processes in achieving proper bioavailability and stability in the pre-formulation stages of the production of solid dosage forms (1). Studies on the discovery of drugs only lead to

the introduction of a new drug substance or chemical entity, and in order to turn it into a pharmaceutical product, it is necessary to combine it with various excipients. Therefore it can be stated that the excipients are inseparable components of pharmaceuticals (2). Interactions between drugs and excipients can lead to

physical or chemical changes in the pharmaceutical product, which are referred to as drug-excipient incompatibilities, and can ultimately affect bioavailability, safety, and efficacy. But despite the vitality of the issue, there is no global standard protocol for examining drug-excipient incompatibilities (2, 3). In recent years, thermal analysis methods have been used to describe and evaluate the compatibility between drugs and excipients in pharmaceutical formulations. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) are the most important thermal analysis techniques in the study of drug-excipient incompatibilities (2-4). The DSC method alone does not eventuate definitive results on drug-excipient incompatibility, but present a very quick and easy technique to check for incompatibility. In studies of incompatibility, it is usually not necessary to use complementary techniques (Due to the complexity and time consuming of them) if there is no incompatibility in the analysis by DSC. But if in the DSC curve analysis shifting to higher or lower temperatures leads to disappearance of certain peaks or generation of new peaks, use of complementary analytical techniques such as XRD (X-ray powder diffraction), NMR (Nuclear magnetic resonance), liquid chromatography, FTIR, etc. may be justified (5). Studies have shown that a change in DSC curves is one of the undoubted signs of interactions between the drug and excipients (6). Isothermal stress testing (IST) is also one of the other methods that include keeping the drug alone and the drug-excipient mixture with or without moisture and at high temperature for a certain period of time (about three to four weeks) to identify any Drug-excipient incompatibility. Serajuddin et. al. adopted one of the IST methods, so that the formulated samples with 20% v/w of added water at 50°C was kept for 1 to 3 weeks (1-3). Sims et. al. then accelerated the method of Serajuddin by changing the temperature to 100°C and the storage time to 1 to 3 days. The DSC method can also be used in conjunction with the IST method to evaluate the compatibility of drugs with selected excipients (2, 3, 7). Fourier-transform infrared (FTIR) spectroscopy is another method for investigating drug-excipient

incompatibilities, which provides information about possible drug-excipient reactions and shows that which chemical groups should be avoided in excipients (8, 9).

Lactose (molecular weight (MW) = 342.3) is one of the most common pharmaceutical excipients that is widely used as a filler or diluent in solid dosage forms (10, 11). Lactose, whether used in hydrous or anhydrous form, does not react with most drugs (12). However, drug substances that have amino functional groups are prone to Maillard reaction with lactose (11, 12).

In 2017, Ghaderi et al. measured the stability of fluvoxamine in samples containing lactose as excipient by DSC, FTIR and mass spectroscopy methods. The FTIR spectroscopy results confirmed the incompatibility of this mixture. To this mixture, 20% v/w water was added and kept at 80°C for 24 hours. The mixture was then injected into a mass spectrometer and Maillard incompatibility was then detected based on mass spectrometry data (13). The researcher and colleagues also identified lactose incompatibility with hydrochlorothiazide. To the above mixture, 30% v/w water was added and placed at 60°C for two weeks. After this period, the structure of two Maillard reaction products containing large amounts of glycosyl amine was identified using liquid chromatography and mass spectrometry (14).

Celecoxib is one of the most important nonsteroidal anti-inflammatory drugs (NSAIDs) and is the first cyclooxygenase 2 (Cox 2) inhibitor which is used to treat various diseases, especially osteoarthritis and rheumatoid arthritis. However, despite the good penetration of this drug into the gastrointestinal tract, the bioavailability of the drug is low, which can be due to the low solubility. This low solubility ultimately leads to insufficient dissolution in gastrointestinal fluids and improper absorption and distribution of the drug in body tissues (15).

Materials & Methods

Celecoxib (4-[5-(4-methyl phenyl)-3-(trifluoromethyl) pyrazol-1-yl] benzenesulfonamide) was obtained from daroopakhsh company. (Tehran, Iran). Lactose monohydrate and KBr powders were

provided from *Merck chemical company*. (*Darmstadt, Germany*).

DSC (differential scanning calorimetry):

Thermal analysis of the drug and the mixture of drug and excipient in 1: 1 w/w ratio were performed by a differential scanning calorimeter (JADE DSC, Perkin Elmer, USA). 5 mg of singular samples of the drug, excipient, as well as drug-excipient mixture, were weighed and placed in the aluminum pan of the DSC apparatus. The heating rate was 10 °C /min and scanned in the temperature range of 25 to 300 °C. The Jade DSC was controlled by Pyris Software.

FTIR (Fourier-transform infrared) spectroscopy:

The FTIR spectroscopy method was used to detect the initial incompatibility. Spectra of pure samples (drug and excipient) and drug-excipient mixture was recorded using FTIR spectrometer (Spectrum Two, Perkin Elmer, USA). Samples (powder and tablet) were incubated at 60°C. FTIR spectroscopy data were obtained and interpreted using the Spectrum Version 10.3.2 software.

Sample preparation:

Initially, equal amounts of celecoxib as drug and lactose monohydrate as excipient were weighed and mixed in a 1:1 ratio in a closed sterile vessel. Then to apply the stress conditions, the weighted samples of drug and excipient were mixed with 20% v/w of sterile distilled water and Vortex for 3 minutes. Finally, in order to evaluate the obtained results, some samples of the pure substance of celecoxib and lactose monohydrate were prepared according to the mentioned method.

Preparation of tablet:

Tablets were prepared by performing direct compression on previously prepared samples.

Results

FTIR (Fourier-transform infrared)

Spectroscopy:

In order to better evaluation and comparing the results, FTIR spectra of celecoxib-lactose powders and tablets at 60°C have been shown in [Figures 1 and 2](#).

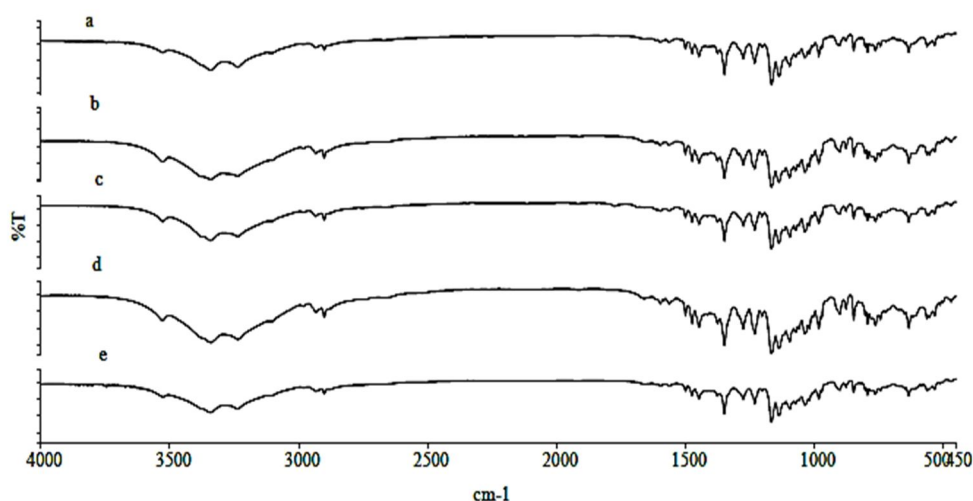


Fig 1. FTIR spectra of celecoxib-lactose powder (from first to fourth week) at 60°C. first day(a), first week(b), second week(c), third week(d), fourth week(e).

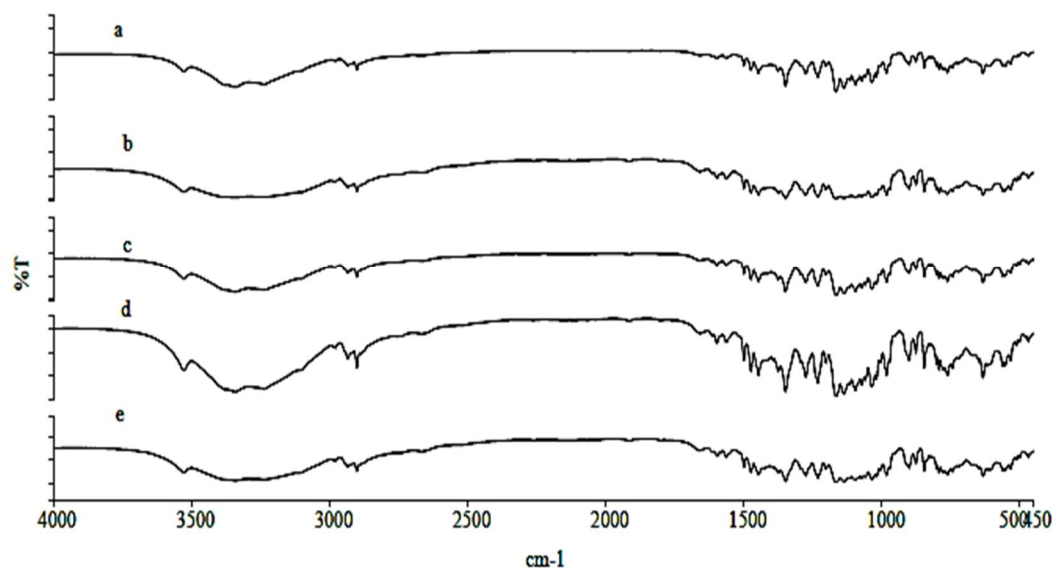


Fig 2. FTIR spectra of celecoxib-lactose tablet (from first to fourth week) at 60°C first day(a), first week(b), second week(c), third week(d), fourth week(e).

At the first day of the test, related to the bands - NH and NH₂, samples of celecoxib before applying the stress conditions, contain absorption spectra of 3348.8 and 3241.2, respectively (17). During the first week of stress at 60 °C, these peaks increased with very small changes to 3345.6 and 3244.9, respectively, which there has been no changes in the relevant functional groups. This stability of peaks was observed after two, three, and four weeks of applying 60°C stress. Also the celecoxib powder in spectral range of 1000-1700 cm⁻¹ has four different peaks, including 1346.8 cm⁻¹ and 1167.8 cm⁻¹, which both correspond to the S = O band and two peaks with wavelengths of 1279.7 and 1235 cm⁻¹, which are characteristic of CF₃ and CN bands (amine group), respectively (17). After one week of temperature stress conditions, no significant changes were observed in the registered peaks compared to first day. This stability and observation of the desired peaks was observed after two, three, and four weeks of continuous 60°C stress and also celecoxib tablets.

Lactose in spectral range of 3300-4000 cm⁻¹ based on the output of FTIR spectroscopy est. Before the application of stress, there were three partial peaks, including 3528.8, 3386.6, and 3341.8. All of these peaks

correspond to the O-H band (17). After a week of stress at 60°C, peaks changed to 3532 and 3394, respectively, but these small changes did not change the original nature of the peaks. This trend was also observed in the following weeks (second, third, and fourth). Lactose tablets also show similar conditions. There was a peak of lactose powder sample in 2905.5 cm⁻¹, which corresponds to the C-H band (17). This stability can be seen in the absorption spectrum in both stress conditions and in the following weeks, as well as in the graphs of the lactose tablet samples.

Differential scanning calorimeter (DSC):

Figure 3. Shows the curves for DSC results of the celecoxib, lactose, and celecoxib-lactose samples. On the thermogram of each sample, the main peaks are also shown.

In thermogram of celecoxib sample, the endometrial peak was observed at 170°C that this peak is related to the melting point of the celecoxib. However, in 2011, Fouad et. al. reported temperature 160°C as endometrial peak of pure drug samples (18). The differences may be due to the difference between the device and the test conditions.

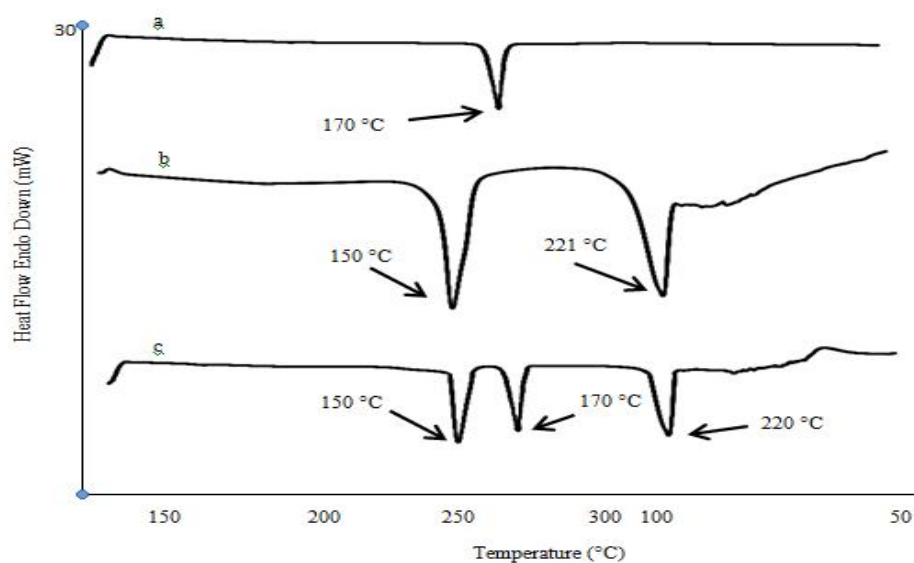


Fig 3. DSC curves of celecoxib (a), Lactose (b), and celecoxib-Lactose (c) Powder samples

Appearance changes:

Figure 4. Shows appearance changes of celecoxib, lactose, and celecoxib-lactose powders, and **figure 5.** Shows appearance changes of celecoxib-lactose tablets

at 50°C and 60°C after four weeks. As it could be seen, there was not any changes in appearance, including discoloration compared to the first day of the test. This could be evidence of drug-excipient (celecoxib-lactose) compatibility.

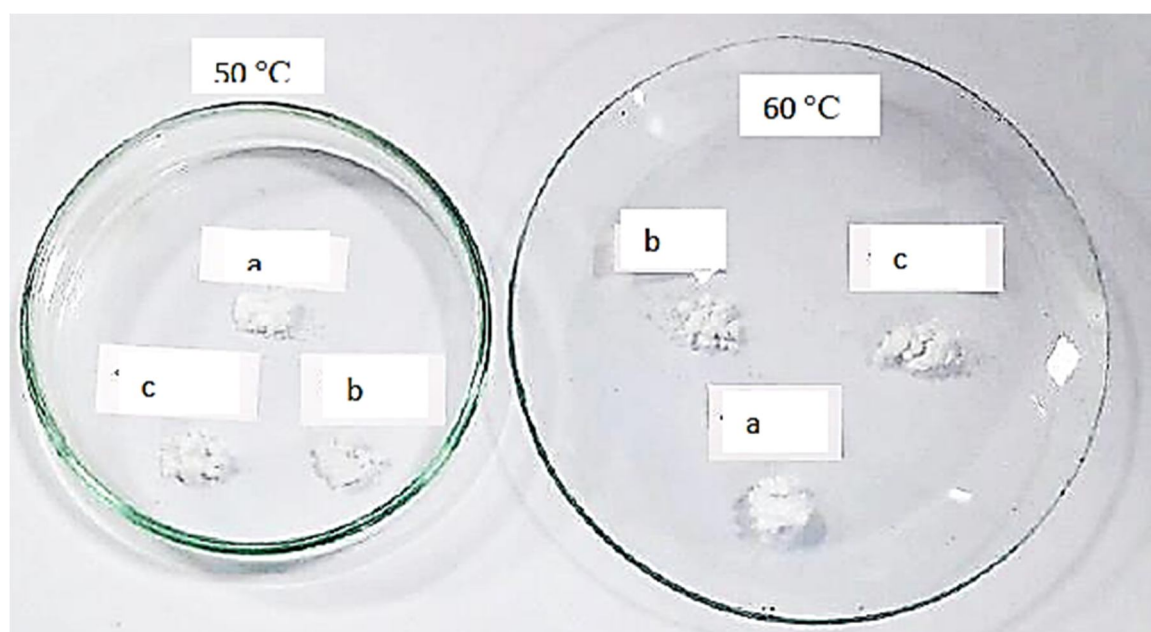


Fig 4. Appearance changes of celecoxib (a), lactose (b) and celecoxib-lactose(c) powders at 50°C and 60°C after four weeks.

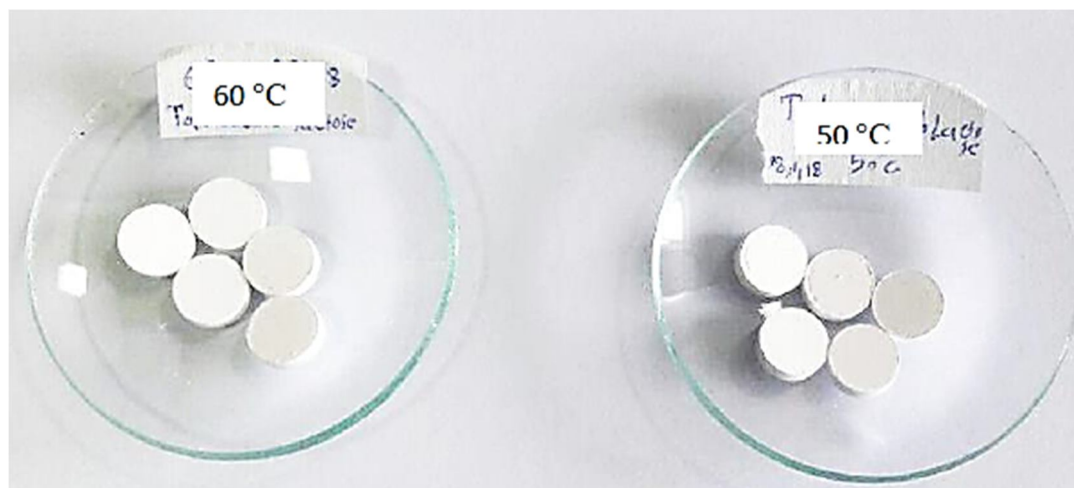


Fig 5. Appearance changes of celecoxib-lactose tablets at 50°C and 60°C after four weeks

Discussion

In the study of the FTIR spectrum of the celecoxib-lactose powder in the range of 3300-4000 cm^{-1} , almost constant conditions without significant changes were observed during the four-week stress conditions at 60°C. As shown in Figures 1. and 2., in the range of 1000-1700 cm^{-1} , there were almost constant conditions without major changes during the four weeks of stress conditions in the studied peaks, which can be detected compared to the first day of the test. Based on all the information from the FTIR spectra of celecoxib, lactose Monohydrate and celecoxib-lactose mixture, no additional peaks in drug-excipient sample has been achieved, and therefore, no changes in the nature of the drug and excipient after four weeks are conceivable. It should also be noted that one of the manifestations of the Maillard reaction is the formation of N=C and/or C=C bands, which are characterized by peaks in 1640-1690 cm^{-1} and 1600-1678 cm^{-1} . None of them were recorded in this study.

In the thermogram of lactose monohydrate sample, endothermic peak can be seen at 150 and 220°C. These peaks are in contradictory with the peaks recorded by Itoh et. al. in 1977 (19). The slight differences are due to working conditions and equipment. These peaks are related to water loss and melting of this excipient, respectively.

In the thermogram of drug-excipient (celecoxib-lactose), all three temperature peaks in both samples are clearly visible. The appearance of these peaks indicates the presence of both test agents in the final sample, without any change in their nature or chemical changes. Overall, the results of DSC indicate drug-excipient compatibility.

Conclusion

In the peaks studied in FTIR spectroscopy analysis of celecoxib sample after stress, no significant change was observed in the recorded peaks compared to the first day. The lactose sample did not show any significant change in the specified peaks after enduring stress. In celecoxib-lactose mixture, all peaks recorded at 60°C on the first day of the test before applying stress conditions can be observed in other weeks. The appearance of these peaks indicates the presence of both functional groups in the final sample

In the thermogram of drug-excipient (celecoxib-lactose) in DSC analysis, all three endothermic peaks of pure drug and excipient are clearly visible in mixture. Also there were no changes in appearance (including discoloration) were observed compared to the first day of the test. By summarizing the above results, it could be stated that due to the lack of additional peaks of drug-excipient sample (celecoxib-lactose) in the FTIR spectrum as well as the lack of removal of temperature

peaks in DSC analysis and the absence of color change in the samples after four weeks, celecoxib as a drug and lactose as an excipient have no incompatibility with each other.

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Conflict of interest

The authors declare no financial or other conflict of interest.

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