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ORIGINAL RESEARCH ARTICLE

Evaluation of Amoxicillin-Lactose Incompatibility Reactions at the Solid-State Using Physicochemical Methods

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Abstract

Background The evaluation of drug-excipient incompatibility is a crucial step in pre-formulation studies, as drug-excipient interaction can have an impact on drug stability and bioavailability. The right selection of excipients is the key to developing successful drug delivery systems or dosage forms. This study is focused on assessing amoxicillin-lactose incompatibility reactions in the solid state through physicochemical techniques.

Methods The mixture of amoxicillin and lactose was made in a 1:1 mass ratio, added to 20% (w/v) water, and kept in closed vials at 60°C. The direct compression method was utilized to prepare amoxicillin, amoxicillin-lactose, and lactose tablets. The manufactured tablets were stored at a temperature of 60°C. Finally, amoxicillin-lactose incompatibility in the solid state was analyzed by Fourier Transform Infrared and differential scanning calorimetry methods over 4 weeks.

Results Physicochemical methods, including differential scanning calorimetry, Fourier Transform Infrared spectroscopy, and visual observation, confirmed incompatibility between amoxicillin and lactose.

Conclusion It is concluded that using lactose in solid pharmaceutical preparations of amoxicillin will result in compatibility problems.

Keywords Amoxicillin, Excipient, Incompatibility, Lactose, Physicochemical, Solid

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1 Introduction

Amoxicillin is an antibiotic drug belonging to the beta-lactam penicillin group. Amoxicillin is used to treat many different types of infections caused by bacteria, such as tonsillitis, bronchitis, pneumonia, and infections of the ear, nose, throat, skin, or urinary tract.

To enhance the formulation, manufacturing process, absorption, administration, appearance, and quality, other components (excipients) are combined with active pharmaceutical ingredients in a dosage form.[1,2]

Although excipients are considered pharmacologically inert, they can participate in chemical or physical interactions with active drug components in the drug products and can have impacts on stability, efficacy, safety, chemical degradation, and dissolution. These interactions could be because of interactions of pharmaceutical ingredients with excipients or inactive impurities.[3-5]

Proper choice of excipients is crucial for the safe and efficient formulation of a drug product that facilitates administration, enhances consumer satisfaction, improves the dosage form's release and bioavailability, and boosts its shelf life.[6,7]

Thus, compatibility studies of drug-excipients are identified as one of the essential phases in the preformulation stage of pharmaceutical manufacturing technology.[8]

Differential scanning calorimetry (DSC), developed by E.S. Watson and M.J. O'Neill in 1962, has been widely used in compatibility studies in pharmaceutical preparations for over 50 years and reveals valuable information including drug purity, drug stability, and polymorphic characteristics.[2,9,10]

Drug-excipient incompatibility researchers used the Fourier transform infrared spectroscopy (FTIR) which is another fast, accurate, and simple technique. Interactions between formulation components may cause changes in the position, intensity, disappearance, and presence of an absorption band in IR spectra.[11]

The Maillard reaction (aldehyde-amine addition) is one of the most important interactions, which is responsible for the incompatibility between reducing sugar excipients such as lactose and dextrose and amine-containing drugs [12,13]

This study is designed to demonstrate the incompatibility of amoxicillin as a primary amine drug with lactose using DSC and FTIR methods. As the Maillard reaction is the most possible incompatibility reaction of amine-containing drugs with reducing sugar, it was predicted that amoxicillin and lactose, as a reducing agent, can undergo an incompatibility reaction. To the best of our knowledge, no previous study has been done on the possible incompatibility of amoxicillin and lactose. These types of research are basic in the pharmaceutical industry.

2 Methods

Materials

Amoxicillin trihydrate [(2S,5R,6R)-6-[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; trihydrate] was obtained from Daana Pharmaceutical Co.(Tabriz, Iran), and monohydrate lactose was purchased from Merck (Darmstadt, Germany)

Methods

Analytical methods

DSC

A differential scanning calorimeter (JADE DSC, Perkin Elmer, USA) was employed to thermally analyze the pure drug, excipient, and drug-excipient physical mixture. An amber glass flask was used to mix equal amounts of amoxicillin and lactose, preparing a binary mixture (10 g) by tumbling to ensure uniformity. An aluminum pan was used to weigh 5 mg of each sample and scan it at a temperature range of 25 to 300°C. Pyris Software was controlled by the Jad DSC.

FTIR

Amoxicillin and lactose were mixed in equal mass proportions (1:1), and following the method by Serajuddin et al., 20% water (v/w) was added to the mixture before storing it in sealed vials. The FTIR spectra were measured and obtained right after mixing and at specific intervals during oven storage, using the potassium bromide (KBr) disc technique (Spectrum Two, Perkin Elmer, USA). The spectrum was generated by averaging ten consecutive scans of the same sample, with a consistent resolution of 4 cm^{-1}. This averaged spectrum was then used for FTIR data processing.

Formulation methods

Preparation of tablets

Equal amounts of amoxicillin as a drug and lactose monohydrate as an excipient were weighed and mixed in a 1:1 ratio and vortexed for 3 minutes. Tablets were prepared by the direct compression method using samples.

3 Results

DSC

The application of DSC in drug-excipient evaluation has been well-established in pharmaceutical preparations for over 50 years due to its cost-effectiveness and convenience. The most important advantage of DSC is

screening potential drug-excipient interaction.[14-16]
Selected DSC curves of the drug, excipient, and drug-excipient mixture are shown in Figure 1. The thermal behavior of net drug, excipient, and binary mixture is compared in the DSC curves.
As shown in Figure 1 the DSC thermogram of amoxicillin showed a melting point at 203.5°C and an endothermic event at 139.8°C, attributed to moisture evaporation.[4,17]
The endothermic peaks of pure monohydrate lactose appeared at 150.3 °C and 220.2°C which are related to the melting of lactose and water evaporation, respectively.[4]
The appearance of a new endothermic peak at 210.1°C in an amoxicillin-lactose binary mixture can only indicate the interaction between the mixture's components.

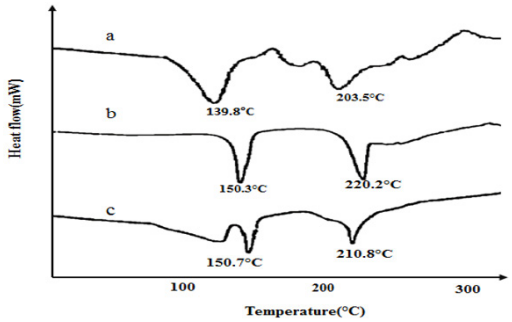

Figure 1 Selected DSC thermogram of (a) amoxicillin, (b) lactose, and (c) amoxicillin-lactose (1:1 W/W) (heating rate = 10°C/ min)

FTIR

Drug-excipient compatibility can be accessed via FTIR based on positional shifts of characteristic peaks, intensity modifications, and the appearance or disappearance of specific absorption bands.[9] To better evaluate and compare the results, FTIR spectra of amoxicillin-lactose powders and tablets at 60°C have been shown in Figure 2 and Figure 3.
The appearance of a new absorption band can be indicative of drug-excipient interaction and provide valuable information about interaction mechanisms.
Amoxicillin IR's main signals revealed principal absorption bands ~ 3550 cm-1 (O—H stretching), 3500 cm-1 (NH2+ due to hydrochloride salt), and principal peaks at wave numbers 1775 cm-1 (C=O stretching vibrations), 1613 and 1684 cm-1 (C = C aromatic stretching vibrations), 1583 cm-1 (C—N stretching).[17]
The main IR signals of lactose were approximately 3459 cm-1, 3292 cm-1, 2811 cm-1 (OH), and 2879 cm-1 (CH2, CH2).
The FTIR results obtained from powder and tablet samples were the same. Amoxicillin-lactose mixture's main signals corresponded to the sum of each component's peaks. In the amoxicillin-lactose mixture, a significant peak was observed at 1690 cm-1 in tablet and powder samples. This vibration can be related to the formation of a C = N covalent band. Controls were done using amoxicillin and lactose pure samples.[2,18] According to the figures for the powder and tablet samples of the mixture kept at 60°C, a peak at 1775 has been eliminated from the first week onwards. This peak is associated with the beta-lactam ring of the amoxicillin structure, the removal of which may indicate the halt of the beta-lactam ring following the reaction of the hydroxyl group of lactose with the amino part of amoxicillin. No change was observed in control samples. As observed in Figure 2 and Figure 3, the FTIR data obtained from the amoxicillin–lactose powder mixture and tablet are the same.

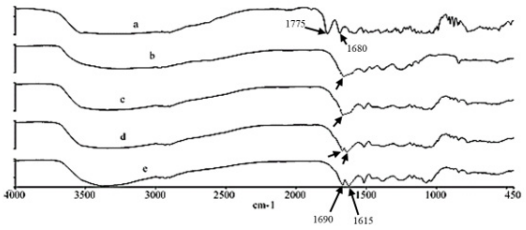

Figure 2 FTIR spectra of amoxicillin-lactose powder (first day (a), first week (b), second week (c), third week (d), fourth week (e)) at 60°C

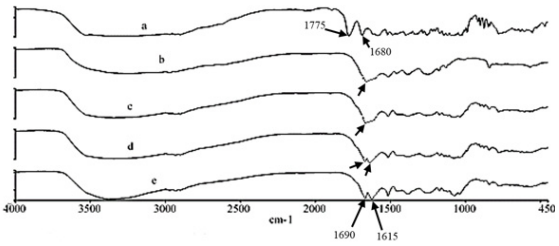

Figure 3 FTIR spectra of amoxicillin-lactose tablet (first day (a), first week (b), second week (c), third week (d), fourth week (e() at 60°C

Appearance changes

The changes in the appearance and color of the powder and tablets during their storage under stress conditions are shown in Figure 4 and Figure 5, respectively.

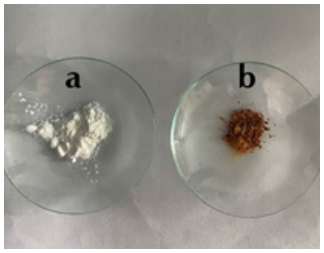

Figure 4 The color changes of the amoxicillin-lactose powder sample from the first day (a) to the fourth week (b) at 60°C

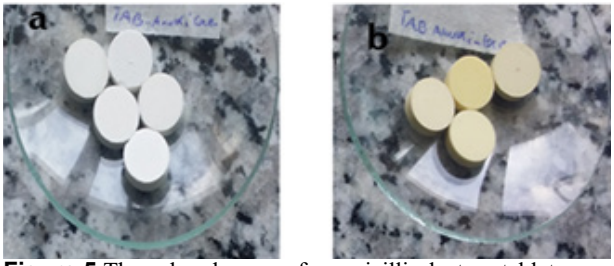

Figure 5 The color changes of amoxicillin-lactose tablets from the first day (a) to the fourth week (b) at 60°C

4 Discussion

5 Conclusion

In this study, the compatibility between amoxicillin and lactose excipient in both powder and tablet forms was examined through DSC and FTIR methods.

In DSC thermal studies, the observation of a change in the melting endotherm of the drug is considered interference. According to the results obtained from the amoxicillin-lactose thermogram, a new peak was generated, possibly due to the incompatibility of the drug and the excipient. [15]

The FTIR spectra should be studied by first analyzing the spectra of the drug and excipient before exposure to stress, and then comparing them with the spectra obtained after stress.

The results demonstrate physicochemical incompatibility between amoxicillin and lactose, evidenced by ETIR and DSC results after 4 weeks of storage.

Based on the obtained results and the change of the main peaks of absorption of the drug-excipient mixture in the fourth week compared to the first day, there is a possibility of incompatibility in the mixture of amoxicillin and lactose.

Also, progressive discoloration (from white to light brown) observed in both powder blends and compressed tablets over the four-week storage period suggests a kind of chemical incompatibility between amoxicillin and lactose.

Declarations

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Artificial Intelligence Disclosure
The authors confirm that no artificial intelligence (AI) tools were used in the preparation of this manuscript.

Authors' Contributions
Not applicable.

Availability of Data and Materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest
The authors declare no financial or other conflicts of interest.

Consent for Publication
Not applicable.

Ethical Considerations
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