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Application of Differential Scanning Calorimetry and Fourier Transform Infrared Spectroscopy to the Study of Metoprolol-Excipient and Lisinopril-Excipient Compatibility

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ABSTRACT

Studies of pharmaceutical drug/active pharmaceutical ingredient (API) compatibility represent an important phase in the design or development of new formulation stage and drug delivery systems. Excipients in the formulations are influenced by the chemical nature, stability, manufacturability, drug bioavailability or delivery of the drug to the patient. Differential scanning calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR) were used as an analytical screening technique for defining the conformity, quality, ability, compatibility of metoprolol and lisinopril with some recently employed pharmaceutical excipients.

Keywords: metoprolol, lisinopril, DSC, FTIR

INTRODUCTION

Studies of actual pharmaceutical drug and active excipient suitability represent a major stage in the design or development of the improvement of all dosage forms or drug delivery systems, one of which is the actual pharmaceutical drug or active pharmaceutical ingredient (API). The possible physical and chemical interactions between drugs and active excipients can affect the chemical structure, stability, manufacturability, bioavailability of drugs or delivery of the drug to the patient and their therapeutic effect and safety [1]. Pharmaceutical drugs and active excipient compatibility studies aids in efficacious dosage form [1-11].

Hypertension is one of the important threats for kidney, stroke and various cardiovascular diseases. Hypertension or high blood pressure is treated by adjusting high blood pressure and body electrolyte balance [12, 13]. Metoprolol is a kind of adrenaline receptor blocker. Lisinopril members angiotensin converting enzyme (ACE) inhibitors and belongs to a group of cardiovascular pharmaceuticals group. They are generally used for the treatment of high blood pressure, angina, arrhythmias, hyperthyroidism, myocardial infarction [14-18]. Excipients can be classified as the basis of their origin, mechanisms and they use in dosage form- functions [19].

In recent years, thermal analytical techniques are widely used in drug excipients compatibility assessment, compound purity, polymorphism, solvation, degradation, and pre-formulation stage. Especially, DSC has been used thermal technique in pharmaceutical drug excipients suitability assessment. DSC is a fast analytical method of evaluating any physicochemical interactions and physical and chemical changes between drug - excipients of the pre-formulation stage. At the end of the study, appropriate excipients are selected [20-23].

FTIR is another analytical technique used in compatibility assessment based on the same functional group change during drug-excipients interaction [24, 25]. If there is band shift and broadening in the functional groups as compared to the spectrum of the pure active drug in the FTIR spectrum, there is an interaction between active drug and excipients [26].

The purpose of the present investigation was to evaluate the compatibility of lisinopril and metoprolol with various active pharmaceutical excipients to be used in the formulations utilizing the different analytical techniques such as DSC and FTIR.

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Table 1. Peak temperature values of metoprolol-excipient physical mixtures

Sample	Drug-excipient ratio	T_{peak} (°C)
Metoprolol	-	126.44
Metoprolol-BHA	1:1	61.74
Metoprolol-CP	1:1	127.67
Metoprolol-cellulose	1:1	126.35
Metoprolol-SCC	1:1	125.62
Metoprolol-sucrose	1:1	126.07
Metoprolol-mannitol	1:1	123.77

EXPERIMENTAL PROCEDURE

Chemicals and Reagents

Metoprolol tartarate and lisinopril were purchased from Sigma Aldrich. Mannitol (Merck), calcium phosphate dibasic (CP, Sigma), sucrose (Merck), butylated hydroxyanisole (BHA, Sigma Aldrich), cellulose (Aldrich), and sodium carboxymethyl cellulose (SCC, Aldrich) were used for the excipients.

Differential Scanning Calorimetry (DSC)

The thermograms of the active drug compund and excipient were obtained using DSC (Perkin Elmer DSC 4000, Waltham, MA, USA) and homogeneous mixture of active drug and excipients in a 1:1 (w/w) ratio. Homogeneous mixture was weighed to about 5-10 mg directly in the pierced DSC aluminum pan [25]. The sample pan was equilibrated heated from - 20°C to 400°C at a rate of 10°C min^{-1} under an atmosphere of dry nitrogen [25-29].

Fourier Transform Infrared Spectroscopy (FT-IR)

IR spectra of the active drug and selected excipient (1:1 ratio, w/w) were recorded on a FTIR spectrophotometer (Perkin Elmer Frontier spectrometer, Waltham, MA, USA) in the range of 4000–500 cm^{-1} [25, 27, 29]. ZnSe-ATR equipment was used as well as KBr pellet technique.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry

The compatibility of metoprolol with the different excipient used such as BHA, CP, cellulose, SCC, sucrose and mannitol was studied using DSC. The thermal curves of metoprolol, the excipient, and the metoprolol-excipient physical mixtures (1:1, w/w) are shown in **Figure 1a**. DSC curve showed an endothermic peak at 126.44°C for metoprolol corresponding to the melting temperature [30] and about the same melting endotherm peak was observed for the other active drug–excipient physical mixtures (123.77°C to 127.67°C for metoprolol-CP (**Figure 1b**), metoprolol-cellulose (**Figure 1c**), metoprolol-SCC (**Figure 1d**), metoprolol-sucrose (**Figure 1e**), metoprolol-mannitol (**Figure 1f**)) (**Table 1**). Because of low-impurities of each component in the mixture, changes in the melting endotherm peak of the metoprolol from 123.77°C to 127.67°C [29, 31, 32] (**Table 1**).

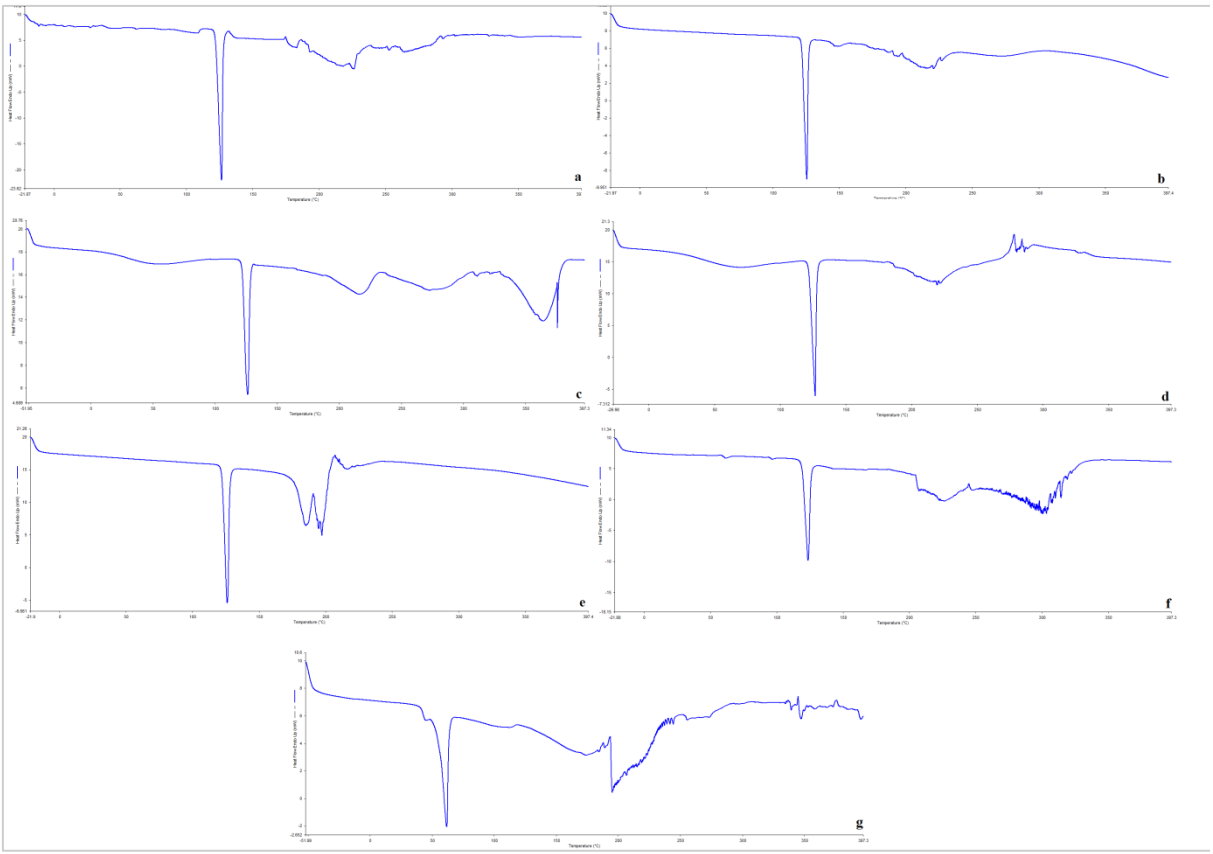

Figure 1. DSC thermogram of a) metoprolol with b) CP c) cellulose, d) SCC, e) sucrose, f) mannitol, g) BHA

Table 2. Peak temperature values of lisinopril-excipient physical mixtures

Sample	Drug-excipient ratio	T_{peak} (°C)
Lisinopril	-	183.24
Lisinopril-BHA	1:1	61.98
Lisinopril-SCC	1:1	183.16
Lisinopril-sucrose	1:1	189.45
Lisinopril-mannitol	1:1	168.28

This result confirms that there is no interaction between the drug and the metoprolol-CP, metoprolol-cellulose, metoprolol-SCC, metoprolol-sucrose, metoprolol-mannitol. The endotherm metoprolol tartrate-BHA at 61.74°C, thus suggesting a probable interaction (**Table 1**; **Figure 1g**).

Lisinopril exhibits a characteristic endothermic peak at 183.24°C corresponding to its melting temperature [30] (**Figure 2a**) and about the same melting endotherm peak was observed for the other active drug–excipient physical mixtures (183.16°C to 189.45°C for lisinopril-SCC (**Figure 2b**) and lisinopril–sucrose (**Figure 2c**)). According to the papers that the minor change in value of the peaks of the DSC thermogram and enthalpy may change due to the entity of low-purity in the compounds used for analysis [29, 31, 32] (**Table 2**). As such there is no interaction between lisinopril-SCC and lisinopril–sucrose.

The endotherm lisinopril–BHA at 61.98°C (**Figure 2d**) and lisinopril-mannitol 168.28°C (**Figure 2e**), thus suggesting a probable interaction.

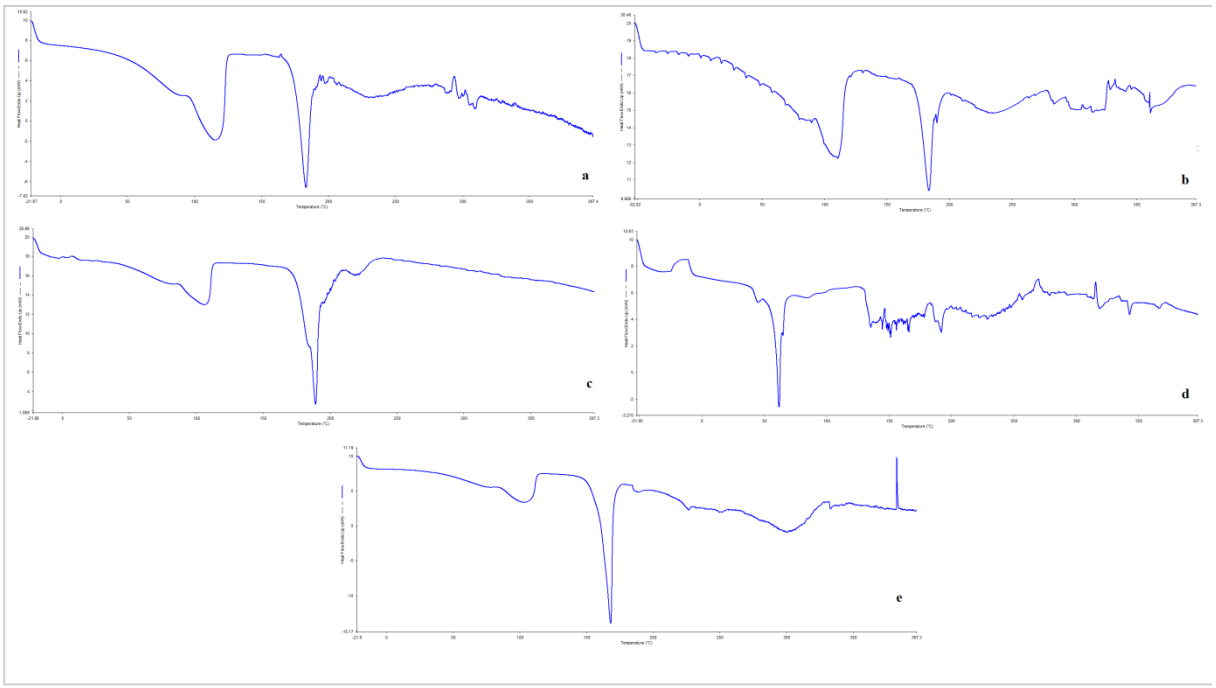

Figure 2. DSC thermogram of a) lisinopril with b) SCC c) sucrose, d) BHA, e) mannitol

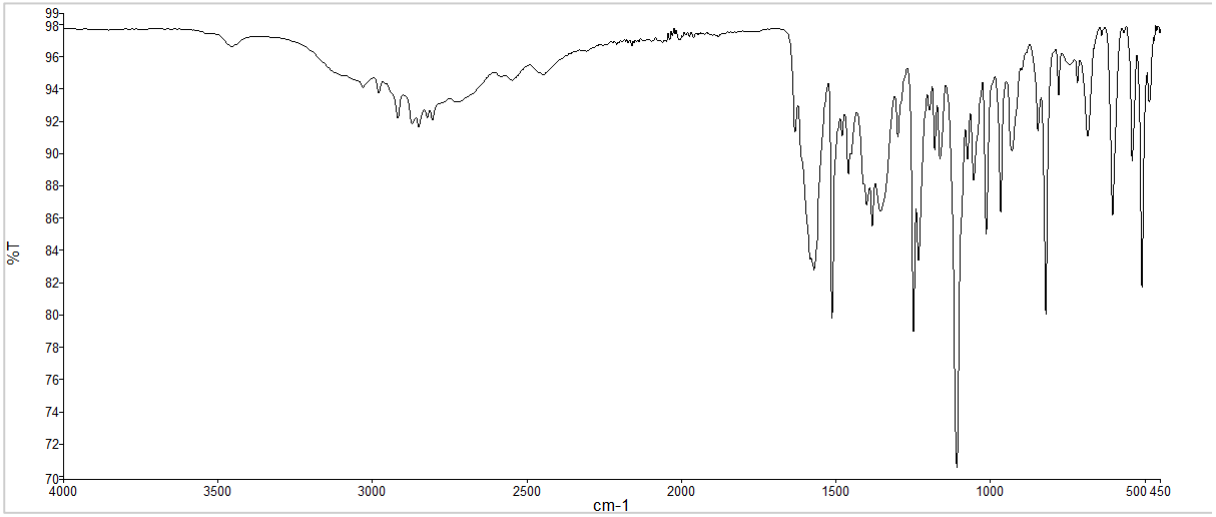

Figure 3. Fourier transmission infrared spectrum of metoprolol

Fourier Tranform Infrared Spectroscopy (FT-IR)

Compatibility between the active drugs and worked excipients used were studied by using FTIR spectroscopy. The use of FTIR spectroscopy technique allows, demonstrating the subsumption of the different functional groups of re-existing and subsequent molecules by analyzing the prominently changes in the shape and position of the absorbance bands.

The FTIR spectrum of metoprolol showed sharp band at 3300 cm^{-1} for –OH stretching vibration and the predominant peak at 3454.18 cm^{-1} for N-H stretching of amino group. The appearance of absorption peak at 3031.51 cm^{-1} was indicative of aromatic –CH stretching vibration. 2917.74 cm^{-1} for aliphatic –CH stretching of methyl group, 1512.91 cm^{-1} for aromatic ring, 1249.01 cm^{-1} for C-O stretching in aromatic ether, 1108.47 cm^{-1} for C-O stretching in aliphatic ether and secondary alcohol absorption, 1249.01 cm^{-1} for C-O stretching in secondary alcohol. Aromatic absorption at 820.52 cm^{-1} and 718.70 for cm^{-1} 1,4-disubstituted benzene. So, spectral placements for significant absorption bands were consistent with the structure of metoprolol [33-35] (**Figure 3**).

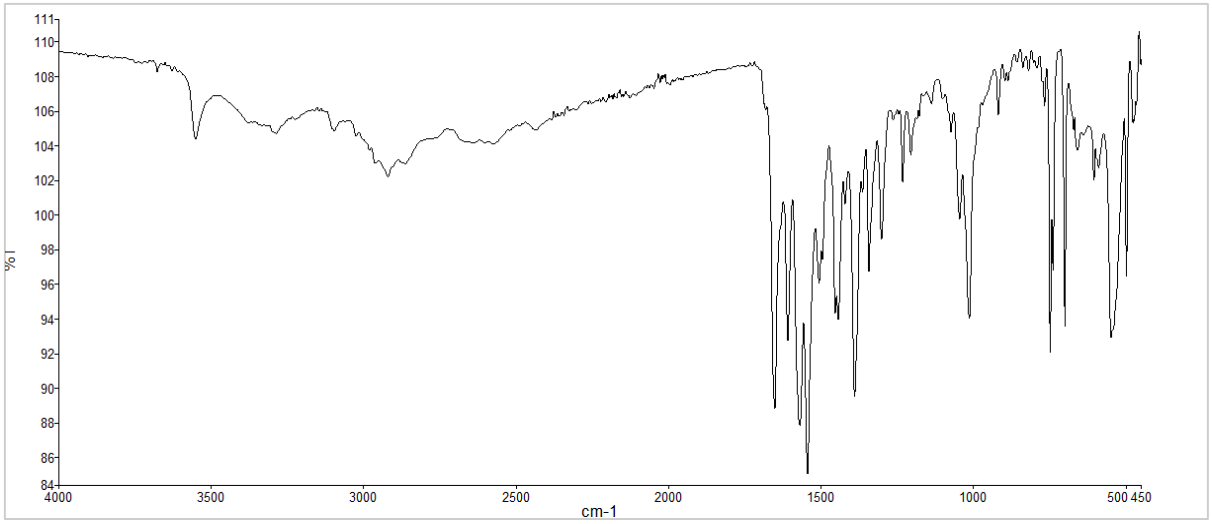

Figure 4. Fourier transmission infrared spectrum of lisinopril

FTIR spectrum of of the active drug-excipient physical mixture, metoprolol-CP, metoprolol-cellulose, metoprolol-SCC, metoprolol-sucrose, and metoprolol-mannitol retained all the characteristic peaks of metoprolol. It was observed that major peak positions for the drug–excipient physical mixtures were totally in adherence with that of observations precludes possible interactions between the active drug and excipients. It can be seen that in the FTIR spectrum of the metoprolol-BHA binary active drug-excipient mix, the drug characteristic peaks either have decreased their intensity along with shifting to varied wavenumbers or have disappeared [36].

FTIR spectrum of pure active drug lisinopril (**Figure 4**) revealed the presence of characteristic peak at around 3554 cm^{-1} is assigned to the stretching vibrations of an O–H band of water. The peaks at 3381 and 3287 cm^{-1} are correspond to the asymmetric and symmetric N–H band of primary amine with hydrogen bonding. The peak at 3095 cm^{-1} is due to the aromatic C–H stretching vibrations around, and the peaks at 2951 and 2919 cm^{-1} are characterized to the asymmetric C–H stretching vibrations, respectively. The peak at around 1652 cm^{-1} is based on the carbonyl stretching of tertiary amide group and/or scissoring NH_2 vibration; that at 1609 cm^{-1} is qualified to the aromatic ring mode, and those at 1559 and 1543 cm^{-1} due to the asymmetric carboxylate and/or ring mode of the aromatic group. The peak around at 1453 cm^{-1} shows the CH_2 scissoring vibration and the peak at 1390 cm^{-1} is due to the symmetric carboxylate [37, 38]. It can be seen that in the FTIR spectrum of the lisinopril-BHA binary active drug-excipient mix, the drug characteristic peaks either have decreased their intensity along with shifting to varied wavenumbers or have disappeared [36].

It was observed that major peak positions for the drug–excipient physical mixtures were totally in respect with that of observations precludes possible interactions between the active drug and excipients.

CONCLUSION

Drug–excipient compatibility studies were completed using different thermal and spectroscopic methods. DSC and FTIR provided useful information on drug–excipient compatibility. From the results of the DSC and FTIR studies an interaction was suspected between metoprolol and BHA. Also, the results obtained from the DSC and FTIR studies showed that the interaction between lisinopril and BHA or mannitol.

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