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Study of Stability and Drug-Excipient Compatibility of Estriol

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Abstract: Estriol, is a major urinary estrogen hormone. Differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR) were used to assess the compatibility between estriol and drug excipients (1:1; w/w). In this study, thermodynamic and spectroscopic data obtained from pure estriol and mixtures of pure estriol with pharmaceutical excipients were compared. Preliminary studies using thermal and spectroscopic technique implied the compatibility of mannitol, calcium phosphate dibasic, sucrose, butylated hydroxyanisole, cellulose, lactose, magnesium stearate, talc and sodium carboxymethyl cellulose with the drug estriol. As a result of the experimental study, there is incompatibility of estriol-mannitol, estriol-sucrose, estriol-lactose and estriol-magnesium stearate.
Keywords: Estriol, Stability Compatibility, DSC, FTIR

1. Introduction

Estrogens are natural endogenous hormones with various physiological effects. Estriol (E3; **1,3,5(10)-Estratriene-3,16α,17β-triol)** is the main estrogen in pregnancy. However, it attracted less attention except pregnancy. Estriol appears to have both estrogenic, antagonistic and agonistic effects. It is mainly secreted by the placenta (Falah et al., 2015). The chemical structure of estradiol is given in Figure 1. Investigation of drug-excipient compatibility is an important step in pre-formulation studies during drug development. Indeed, interactions between potential physical and chemical drugs and excipients increase the chemical structure, stability and bioavailability of the drug. This may affect the efficacy of the drug (Oliveira et al., 2010, Soares et al., 2011, Soares-Sobrinho et al., 2010, Tita et al., 2011, Verma et al., 2005, Viana et al., 2008).

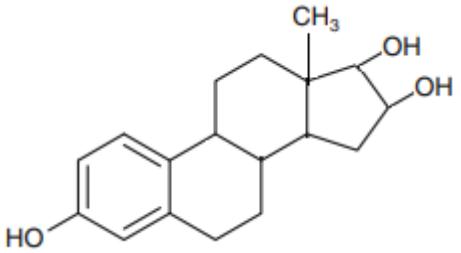

Figure 1. The chemical structure of estriol

There are two types of chemical incompatibilities in the literature. First, excipient-induced structural degradation of the drug, such as oxidation or hydrolysis; the second is a covalent reaction between the drug and the excipient (Brown et al., 1998, Pyramides et al. 1995, Giordano et al. 1988, Bruni et al.2002, Mura et al.1995, Cunha-Filho et al. 2002).

Differential scanning calorimetry (DSC) is widely used to evaluate the physical properties of drugs, including melting and evaporation temperatures, to

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determine glass transition temperatures and to examine stability. DSC is a technique that allows rapid assessment of possible discrepancies by revealing changes in the corresponding reaction enthalpies in appearance, shifting or disappearance of melting or other exothermic processes (Brown et al., 1998, Pyramides et al. 1995, Giordano et al. 1988, Bruni et al.2002, Mura et al.1995, Cunha-Filho et al. 2002, Wesolowski et al. 1992, Joshi et al. 2002, Monajjemzadeh et al 2009).

FTIR is another effective analytical technique used in the assessment of compatibility based on the same functional group change during the interaction between the drug and the drug excipients (Joshi et al. 2002, Monajjemzadeh et al 2009). The location and structure of the functional groups in the spectra of pure drug and drug-excipient mixtures are compared. If there is band shift and widening in the spectra, there is an interaction between active drug and excipients (Swathi et al. 2017).

In the present study, the possible interactions between estriol and excipients (mannitol, calcium phosphate dibasic, sucrose, butylated hydroxyanisole, cellulose, lactose, magnesium stearate, talk and sodium carboxymethyl cellulose) have been evaluated. For this purpose, DSC and FTIR measurements were carried out on each of the components, both in the pure form, in some of the corresponding solid binary mixtures estriol/excipient.

2. Material and Method

2.1. Chemicals and reagents

Estriol was purchased from Sigma Aldrich. Mannitol (M, Merck), calcium phosphate dibasic (CP, Sigma), sucrose (S, Merck), butylated hydroxyanisole (BHA, Sigma Aldrich), cellulose (C, Aldrich), lactose (L, Sigma Aldrich), magnesium stearate (MS, Sigma Aldrich), talc (T, Sigma Aldrich), and sodium carboxymethyl cellulose (SCC, Aldrich) were used for the excipients.

2.2. Methods

A differential scanning calorimeter (DSC, Perkin Elmer DSC 4000, Waltham, MA, USA) was used for the thermal analysis of the drug and mixtures of the drug and the excipients in a 1:1 w/w ratio. Individual samples of the drug and the selected excipients were weighed to approximately 10 mg in a DSC aluminum pan and scanned in the temperature range of -20–400°C under an atmosphere of nitrogen. The heating rate was 10°C min^{-1}, and the obtained curves were observed for any type of interaction. Enthalpy calculations were completed using Pyris software (Monajjemzadeh et al 2009, Swathi et al. 2017, Bozdağ-Pehlivan et al. 2011, Wakasawa et al 2008, Pani et al. 2011).

FT-IR spectroscopy using KBr-pressed disk technique was conducted on a Frontier spectrometer (Perkin Elmer Frontier spectrometer, Waltham, MA, USA). 10 mg of drug and drug-excipient mixture samples and 100 mg of potassium bromide were weighted, ground in an agate mortar, and pressed for 10 minutes at approximately 10 tones/cm^2 to form a semitransparent pellet which lets light to be transmitted to the detector (Monajjemzadeh et al 2009, Bozdağ-Pehlivan et al. 2011, Pani et al. 2011).

3. Results and Discussion

3.1. Differential Scanning Calorimetry

The compatibility of Estriol with the different excipient used M, CP, S, BHA, C, L, MS, T, and SCC were studied using DSC. DSC curve showed an endothermic peak at 288.97°C for Estriol corresponding to the melting temperature point. Similar melting endotherm peak was observed for the other active drug–excipient physical mixtures (287.19°C to 285.29°C for Estriol-CP, Estriol-BHA, Estriol-C, Estriol-T, and Estriol-SCC (Table 1). The low impurities of each component in the mixture caused a slight change in the melting endothermic peak of estriol (287.19°C to 285.29°C) (Table 1).

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

Sample	Drug-excipient ratio	T_{peak} (°C)
Estriol	-	**288.97**
Estriol-M	1:1	**170.96**
Estriol-CP	1:1	**285.36**
Estriol-S	1:1	**192.94**
Estriol-BHA	1:1	**285.29**
Estriol-C	1:1	**287.19**
Estriol-L	1:1	**215.21**
Estriol-MS	1:1	**277.93**
Estriol-T	1:1	**286.83**
Estriol-SCC	1:1	**285.67**

This result confirms that there is no interaction between the Estriol and CP, BHA, C, T, and SCC, The endotherm of Estriol-M at 170.96°C; Estriol-S at 192.94°C; Estriol-L at 215.21°C and Estriol-MS at 277.93°C. This is indicative of a possible drug-excipient interaction.

3.2. Fourier Tranform Infrared Spectroscopy (FT-IR)

In the second stage of the study, the compatibility between estriol and the excipients used was examined using FTIR spectroscopy. In the FTIR spectroscopy technique, significant changes in the shape and position of the absorbance bands are analyzed. The FTIR spectrum of pure estriol is shown in Figure 2.

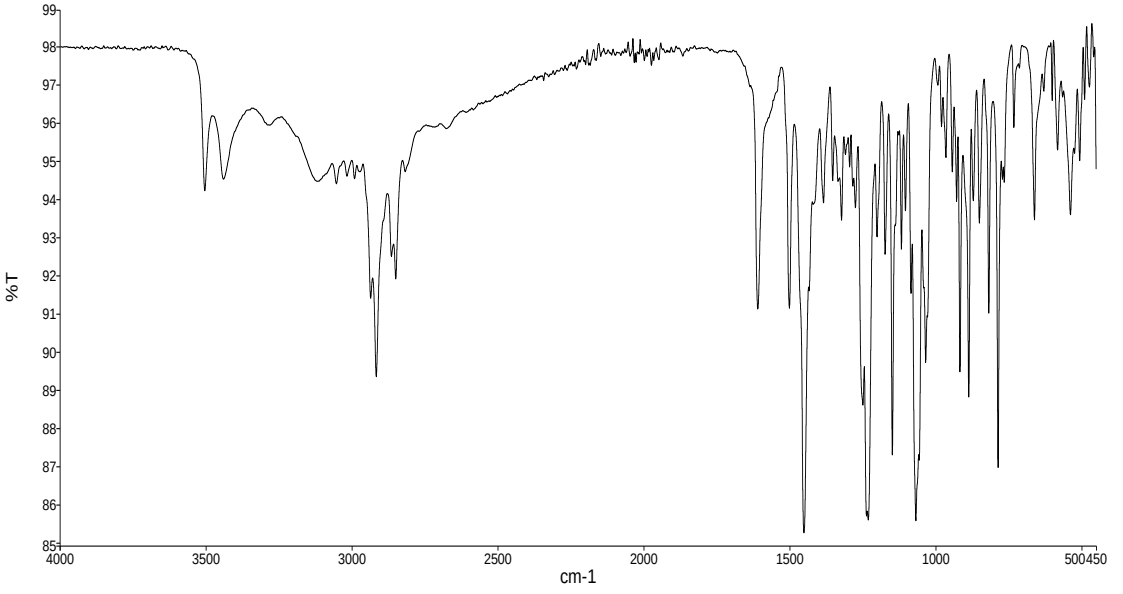

Figure 2. Infrared spectrum of estriol in KBr

The description of the peaks is given in Table 2.

Table 2. The FTIR description of estriol

Group	Wavenumber (cm^{-1})
Symmetric and asymmetric CH_2 peak	3505 nm and 3440 (Fioravanti et al. 2016)
C–H stretching	3000–3100 (Minaeva et al, 2008)
Stretching C-H vibrations in CH_3, CH_2 and CH groups	2936-2818 (Minaeva et al, 2008)
Skeletal vibrations of the aromatic C–C bonds	1609-1501 (Minaeva et al, 2008)
Polar C–O bond in phenols	1231-1148 (Minaeva et al, 2008)
C–O stretching vibrations of secondary alcohols	1125–1030 (Minaeva et al, 2008)

In our study, FTIR spectroscopy was used as the second technique to see the interaction between estriol and excipients. It analyzes significant changes in the shape and position of the absorbance bands to show the assumption of different functional groups of present and subsequent molecules.

FTIR spectrum of of the active drug-excipient physical mixture, for estriol-CP, estriol-BHA, estriol-C, estriol-T, and estriol-SCC retained all the characteristic peaks of estriol (Figure 3).

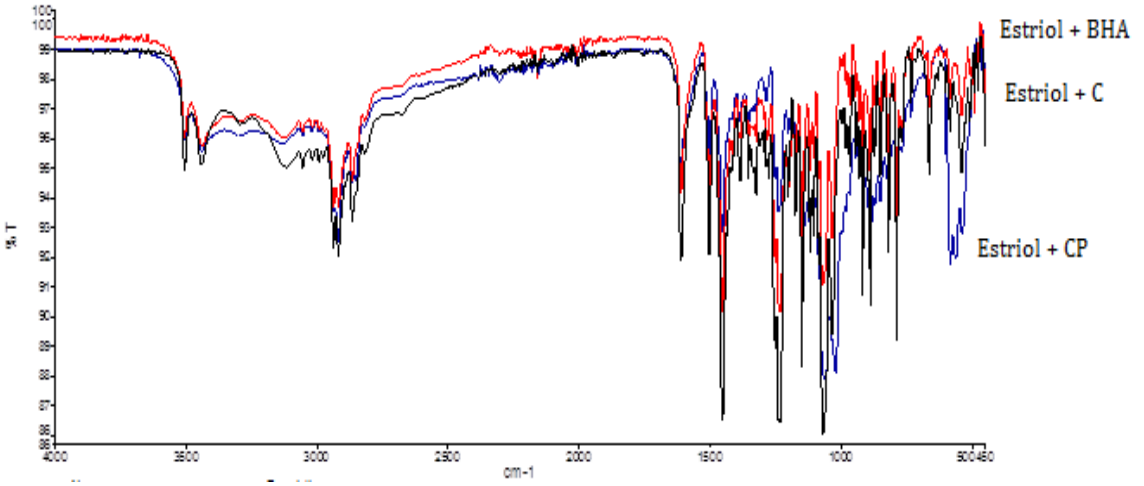

Figure 3. FTIR spectrum of estriol+BHA, estriol+C and estriol+CP in KBr

It can be seen that in the FTIR spectrum of the estriol and M, S, C, L, and MS binary active drug-excipient mix, the estriol characteristic peaks either have decreased their intensity along with shifting to varied wavenumbers or have disappeared (Figure 4).

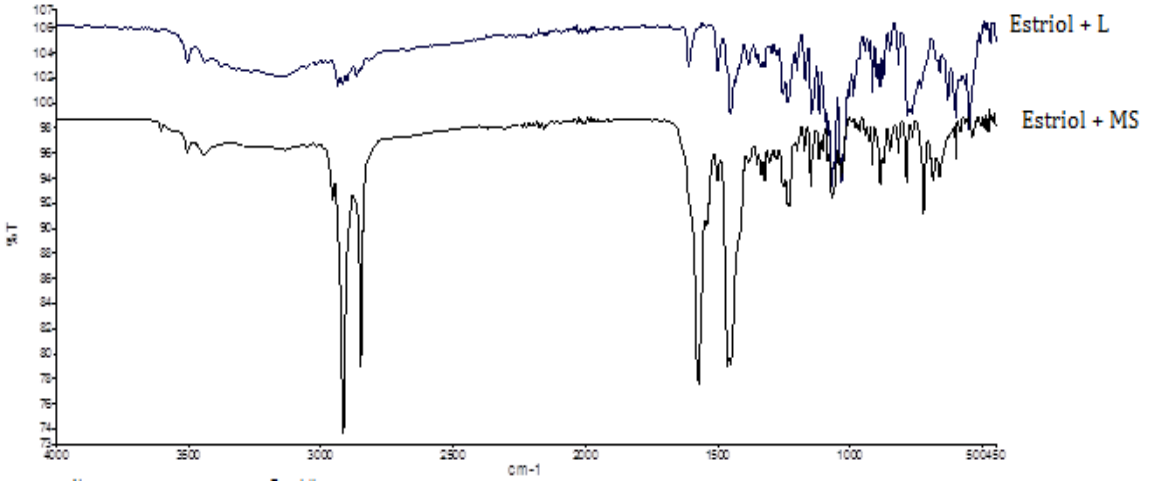

Figure 4. FTIR of estriol+L, and estriol + MS in KBr

4. Conclusion

In our study, estriol-excipient compatibility studies were performed using different thermal and spectroscopic methods. The most commonly used techniques in such studies are DSC and FTIR. These two techniques provide useful information about drug-excipient compatibility. The results of DSC and FTIR studies were suspected to be an interaction between estriol and M, S, C, L, and MS.

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