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Solid State Compatibility Studies of Miconazole Using Thermal and Spectroscopic Methods

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Abstract Drug excipient physicochemical characterization is a systematic approach towards design of therapeutically active and stable dosage forms. The rapid advancements in novel drug delivery systems have led to an interest by formulation scientists in the role and functionality of the excipients. Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC), and Powder X-ray diffractometry (XRD) analytical techniques of high resolution were used to get an insight on solid state properties of the drug and evaluate drug-excipient compatibility. Preformulation studies which were performed using thermal and spectroscopic techniques implied compatibility of phospholipon 90, cholesterol and carbapol 934 excipients with the drug miconazole nitrate.

Keywords Preformulation, Incompatibility, Excipient, Thermal analysis, X ray Diffraction

1. Introduction

Estimation of drug-excipient interactions is a pivotal step in preformulation studies of drug development to achieve consistent stability, bioavailability and manufacturability of vesicular dosage forms. The advent of analytical methods like FTIR spectroscopy, DSC and X ray diffraction into pre-formulation studies have contributed significantly to early prediction and characterization of pharmaceutical excipients' incompatibility with active pharmaceutical ingredient(API) to avoid expensive material wastage and considerably reduce the time required to arrive at an appropriate formulation [1, 2]. The present research article focuses on the analytical techniques for compatibility screening of miconazole nitrate with cholesterol (CHL), phosphatidylcholine (P90) and carbopol (C 934) using DSC, nonthermal FTIR and XRD techniques for development of targeted nano drug delivery systems.

Miconazole Nitrate: Chemistry and Action

Miconazole nitrate (MN) has a broad spectrum and inhibits the growth of dermatophytes, namely, species of *Trichophyton, Microsporum, Epidermophyton,* pathogenic and nonpathogenic yeasts, and gram positive bacteria. Miconazole nitrate ([1-2(2,4-dichlorophenyl)-2-(2,4-dichlor ophenyl) methoxylethyl imidazole) contains a five membered ring imidazole containing 2 nitrogen atoms (Figure 1).

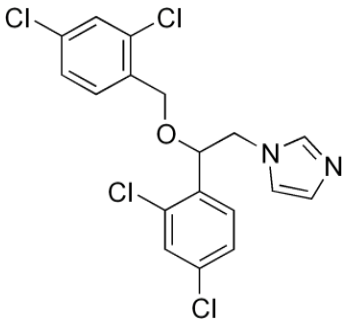

Figure 1. Chemical Structure of Miconazole

The basic N3 atom of the azole forms a bond with the heme iron of CYP 450 prosthetic group and remainder of the azole antifungal forms bonding interactions with the apoprotein in a manner that determines the relative selectivity of the drug for the fungal demethylase. Miconazole inhibits 14α-demethylase which results in accumulation in the fungal cell membrane of sterols still bearing a 14α-demethyl group. These sterols do not have the exact shape and physical properties of the normal membrane sterol ergosterol. This results in permeability changes, leaky membranes and malfunction of membrane-imbedded proteins. Thus this antifungal agent inhibits ergosterol biosynthesis in fungal cell membrane which changes membrane integrity and fluidity thus causing lysis of fungal cell membrane (Figure 2). These effects taken together lead to fungal cell death.

Recently an additional fungicidal mode of action for miconazole has been identified according to which, MN damages actin cables and causes reactive oxygen species induction within fungal organism, thus causing oxidative damage and cell death [3].

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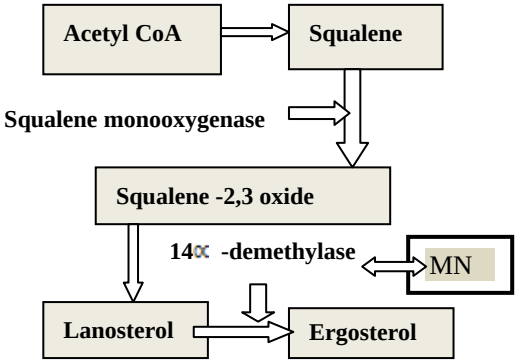


Figure 2. Inhibition of Ergosterol Synthesis by Miconazole Nitrate

2. Materials and Methods

The drug miconazole nitrate was obtained as a gift sample from GlaxoSmithKline Pharma Ltd., Mumbai. Cholesterol (Lobachemie), Polymer-Carbapol 934 (HPL Chemicals) were used in the study. Phospholipon 90 (phosphatidylcholine) was obtained as a kind gift from Lipoid GmbH, Ludwigshafen, Germany. All the chemicals and solvents used in the study were of analytical grade.

2.1. Differential Scanning Calorimetry

DSC analyses of pure drug MN and excipients - CHL, P90 and C934 were performed on a DSC-25 Mettler (Perkin-Elmer Pyris 1). Samples were weighed accurately (~3-5 mg) in aluminum pans and heated at a predefined rate of 10℃/min over the temperature range from 20 to 300℃ in nitrogen atmosphere. Nitrogen gas was introduced at 2 bars and flow rate of 20 mL min^{-1}. On the other side of calorimeter, an empty crimped aluminium pan was placed as a reference standard. The scans were recorded and plots between heat flow and temperature (℃) were obtained [4, 5].

2.2. Infrared Spectroscopy (FTIR)

FTIR spectra of pure drug MN, carbopol 934 polymer, lipid phosphatidylcholine and cholesterol (CHL) were recorded using KBr pellet technique (2 mg sample in 180 mg KBr) on an IR spectrophotometer (Perkin Elmer, Japan) over a range 400-4000 cm^{-1} [6].

2.3. X-ray Diffraction Study (XRD)

XRD solid state analysis of the pure drug was done using X-Ray Diffractometer (X'PERT Pro Holland).

The powder was fixed on to X-ray diffraction slide and fitted into a sample holder on X-ray diffraction machine. The diffractogram were recorded on X'PERT Pro PANalytical 3040/60 Diffractometer (Netherland, Holland) using Cu-Kα line as a source of radiation which was operated at the voltage 40 kV and the 30 mA [7]. All samples were measured in the 2θ angle range between 5-40° with scanning rate 2° min^{-1}.

2.4. Drug–Excipient Compatibility Study

As a part of pre- formulation study, a compatibility study of MN with the other excipients was carried out using physical blends in IR spectroscopy and DSC thermal analysis as mentioned above [8]. In IR spectroscopy, 1:1 proportion of solid state drug with excipients was checked for by observing the functional peaks of drug (characteristic wave numbers) in physical mixtures. DSC studies were done to evaluate drug excipient interaction and change in position of endothermic peak in drug blend. X ray diffraction spectra of drug polymer mixture was obtained for investigating the crystallinity of the drug in polymer mixture.

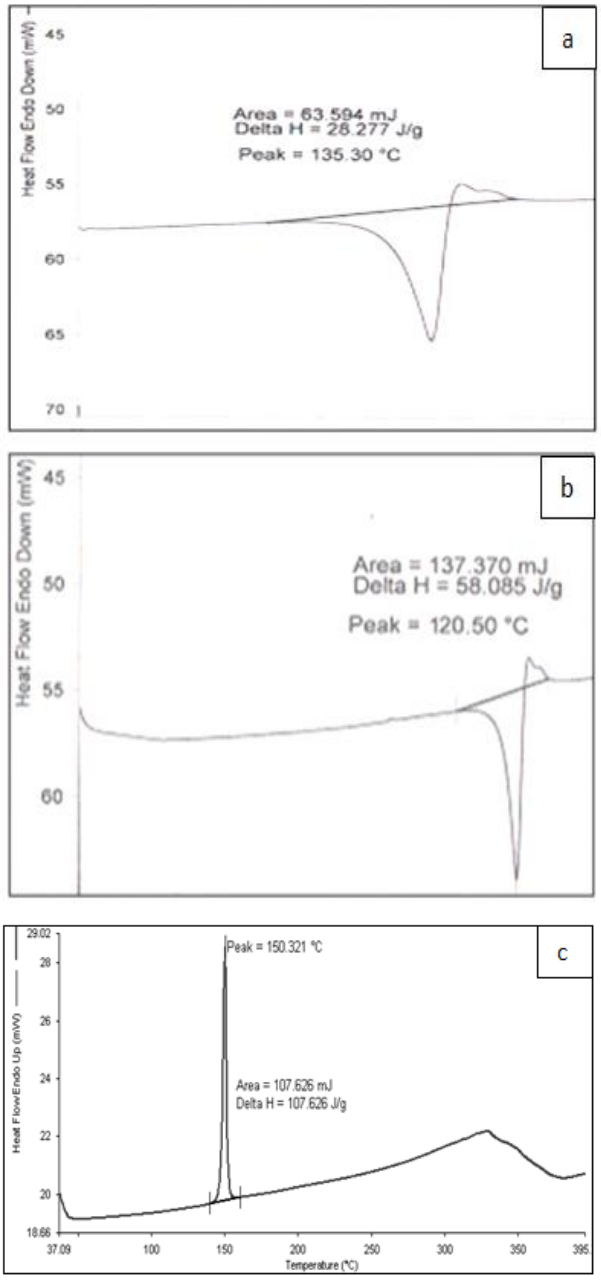
3. Results and Discussion

The rapid evolution of delivery systems, advancements in biopharmaceutics and drug development, scientific, regulatory and economic factors have led to a new interest in characterization of excipients. More than hundreds of excipients with varying simple to complex chemical structures are available from a multitude of sources and are used today in the pharmaceutical industry [9]. Excipients when added in drug delivery system perform a variety of functions to guarantee bioavailability of the drug substance from the drug product, stability of delivery system and its manufacturability on a production scale [10]. For the development of targeted release formulations of miconazole nitrate, various analytical techniques were used to assess the compatibility of miconazole nitrate with selected excipients [11, 12].

Differential Scanning Calorimetry (DSC) studies were carried out using DSC-25 Mettler which is a very useful thermoanalytical tool to evaluate purity and physicochemical state of compounds using melting point and enthalpy changes of physical blend for drug excipient interaction [13]. This analytical technique measures the heat flow rate to or from a sample specimen as it is subjected to a controlled temperature program in a controlled atmosphere. In heat flow curves, peak transitions are associated with melting, crystallization, and curing. The main benefit of DSC, rather than stressed storage methods, is its ability to quickly screen potential recipients for incompatibilities derived from the appearance, shifts or disappearances of peaks and/or variations in the corresponding enthalpy of transition. Also other features like low sample usage also makes it an attractive method [14].

The thermograms of MN, CHL, P90 and C934 were obtained in which Y-axis represented heat flow in milliWatts (mW) and the X-axis displayed temperature (T) (Figure 3 a, b, c, d). When DSC scan of the drug was performed; a peak was obtained at 135.3℃ that confirms the melting point of MN. CHL showed a sharp endothermic peak at 150.3 ℃ which corresponds to its melting point. Carbapol 934 showed two broad endothermic peaks, one at 76.26℃, and the other one at 238.9℃. The thermogram of PL90 showed

slightly sharp peak at 120.5℃. This study further was aimed to evaluate physical mixture of drug with cholesterol and phospholipon 90 (1:1 w/w) for any evidence of interaction. The thermogram of physical mixture showed peaks at122.4℃ (corresponding to PL 90), at 135.3℃ (corresponding to MN) with enthalpy changes and at 150.6 ℃ and 160.8 ℃ (corresponding to CHL) (Figure 3e) As position of endothermic principal peak of drug is observed at 135.3°C in solid state thermal screening, drug was found to be compatible with excipients and there was no appreciable change observed in melting endotherm of physical mixture corresponding to pure pharmaceutical ingredients.



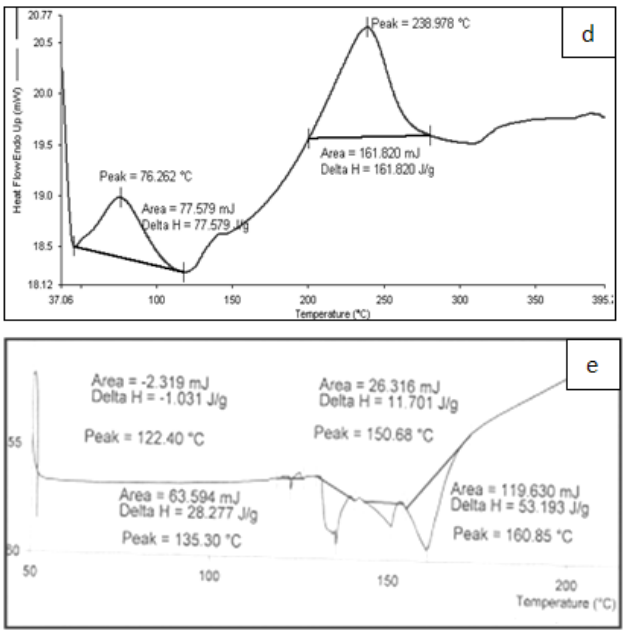


Figure 3. Differential Scanning Calorimetry Thermograph of a.MN b .P 90 c. CHL d. C 934 e. Drug: P90: CHL Physical Blend

Infrared spectroscopic studies are very helpful in the analysis of purity of chemical compounds. The samples of drug and excipients were scanned in the region 4000-400cm^{-1} with a resolution of 4cm^{-1}. Major bands were identified due to specific functional groups in the compound. % Transmittance was plotted on y-axis and wave number on x-axis. Band positions in IR spectra is expressed as wave number and band intensity is expressed as transmittance. The FTIR spectra details of mixture of drug and excipients is shown in (Table 1). The spectrum of pure MN presented characteristic peaks at 3180 cm^{-1} (Imidazole C-N stretching), 3107 cm^{-1} (aromatic CH stretching), 2960 cm^{-1} (aliphatic CH_2 stretching), 1589 cm^{-1} (C=C aromatic), 1385 cm^{-1} (C-H bending),1330 (C-N stretching) and 1012 cm^{-1} (C-C stretching). From the (Figure 4), it was observed that the drug shows characteristic peaks and there were no significant changes in the position of the characteristic peaks of drug when mixed with P 90, CHL and C934, which indicated compatibility of excipients with drug.

X-ray diffractometer consist of three basic elements: an X-ray tube, a sample holder and an X-ray detector. X rays generated in cathode tube of diffractometer on applying voltage leads to electrons generation which are directed to the sample in holder. The geometry of an X-ray diffractometer is such that the sample rotates in the path of the collimated X-ray beam at an angle θ while the X-ray detector is mounted on an arm to collect the diffracted X-rays and rotates at an angle of 2θ [15]. When the geometry of the incident X-rays impinging the sample satisfies the Bragg Equation, constructive interference occurs and peaks are formed which are measured in terms of intensity [16]. The X-Ray diffractogram of miconazole nitrate demonstrates

sharp and narrow peaks at diffraction angles 9.36º, 13.05º, 15.59º, 16.22º, 18.55º, 20.80º, 21.57º, 22.95º, 27.32º, 29.9º, 31.82º, 36.6º which shows a typical crystalline pattern (Fig 5). There are no differences in intensities and sharpness in peaks of drug in corresponding physical polymer mixture and almost similar pattern of peaks is retained. Also no superimposition effect of polymer or peak attenuation is observed on drug pattern.

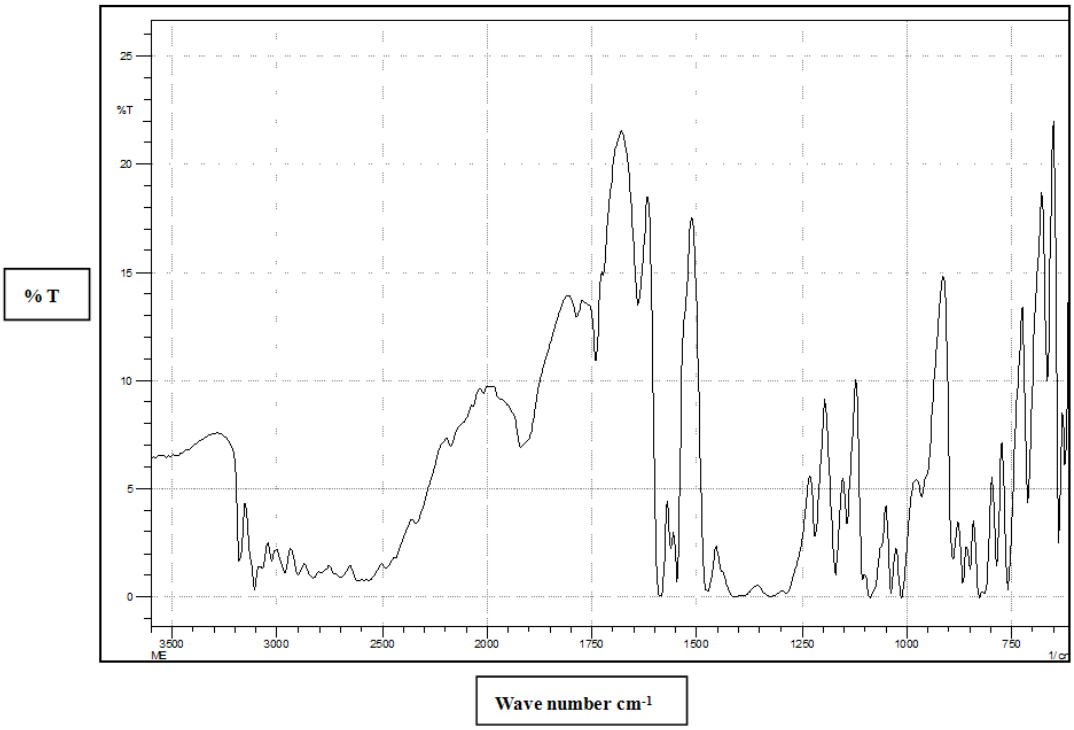


Figure 4. FTIR of MN (Principal peaks at 3180, 3107, 2960,2900,1919,1589, 1012,758 cm^{-1})

Table 1. IR Spectroscopic Analysis and Peak Wave Numbers of Pure Drug MN and of MN in Binary Mixture (cm^{-1})

No	MN	MN : P90	MN: CHL	MN: C934	Functional Groups
1	3180	3183	3184	3183	Imidazole CN stretching
2	3107	3107	3108	3107	Aromatic CH stretching
3	2960	2957	2932	2960	Aliphatic CH_2 stretching
4	1589	1587	1588	1587	C=C aromatic
5	1385	1384	1384	1385	C-H bending
6	1330	1329	1330	1329	C-N stretching
7	1012	1015	1015	1011	C-C stretching
8	758	761	761	761	C-H bending (aromatic)

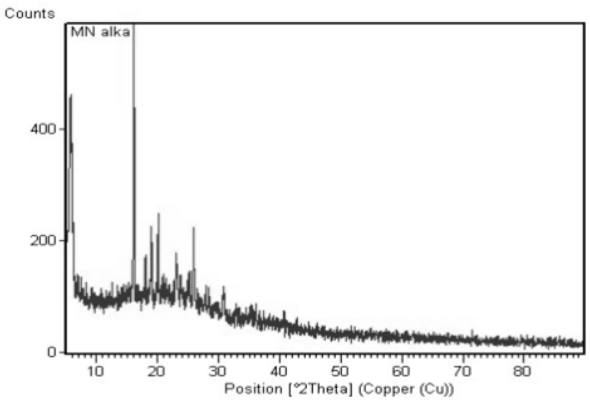


Figure 5. X Ray Diffractogram of Miconazole Nitrate

4. Conclusions

In order to prepare a physically and chemically stable formulation, it is necessary that the drug should be compatible with the excipients that are intended to be used in the formulation. Differential calorimetric analytical studies have shown that miconazole nitrate is very much compatible with selected additives-lipid, polymer and membrane stabilizer. The complementary techniques-XRD, FTIR further confirmed the findings of thermal analysis. Thus, promising results of solid state compatibility screening analysis of drug and no excipient interaction indicate suitability of pharmaceutical ingredients for development of targeted nano drug delivery systems.

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