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PREFORMULATION STUDIES TO DESIGN AND DEVELOP LULICONAZOLE TRANSFEROSOMAL PATCH

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Abstract

The purpose of pre-formulation is to ensure that a pharmaceutical dosage form will be created under the ideal conditions for material processing in order to achieve the performance and stability required. The main objective is to examine the possible luliconazole drug-excipient interactions and determine whether they are compatible with the formulation of transferosomal patches. For the transdermal medication delivery system to be stable and prosperous, it is essential to comprehend the following interactions like Solubility, Melting point, Partition coefficient, Spectroscopy and their compatibility studies such as Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Colorimetry (DSC) among the chosen excipients and these are just a few of the experimental studies done to define the physio-chemical properties of luliconazole. The results for the luliconazole's solubility, melting point, and partition coefficient were satisfactory. The FTIR spectra of luliconazole had distinctive spectra at 3112 cm^{-1} (CH aromatic stretching), 3041 cm^{-1} (C═C aromaticring), and 1326 cm^{-1}(SH stretching), which were frequently present in all physical mixtures examined. There was no interaction in the drug's characteristic peak after mixing, the investigating spectra acquired a statement to that effect. On the basis of DSC results, luliconazole has been noted to be compatible with the selected excipients.

Keywords: Luliconazole, Transferosomes, UV- Spectroscopy, FTIR, DSC.

INTRODUCTION

Pre-formulation refers to the process "Prior to the compounding of the dosage form".Preformulation studies are an essential method for determining the drug's chemical and physical properties [1,2]. The drug's characteristics have a significant impact on the

processing parameters, including the formulation's pharmacokinetic response, compatibility, entrapment efficiency and preparation technique. Excipients are required to promote uniform release, enhance bioavailability, speed up drug administration, and protect active substances from the environment. In order to achieve consistent stability while minimising development time and costs, estimating drug-excipient interaction is essential at the drug development stage. Substances frequently interact chemically and physically[3,4]. Luliconazole(Luz) is a topical antifungal medication that falls within the dichlorobenzene class of substances. It has an optically active R-isomer and a wide range of activity. Luliconazole was approved by the USFDA in November 2013. Luliconazole acts by prevent the synthesis of ergosterol, an essential component of fungal cell membranes by inhibiting both lanosterol demethylase and the cytochrome P450 2C19 enzyme[5,6].Transferosomal patches are primarily designed to increase penetration and the ability of the drug to localise, sustain its action at the site.

Therefore, the aim of this research was to investigate a fewphysiochemical characteristics of luliconazole that can be used to determine future approaches for formulating transferosomal patches meant for transdermal application.

Preformulation studies have been performed for identification (physical characteristics, melting point, and UV spectrophotometric analysis), solubility, lipophilicity (partition coefficient determination), compatability using Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) for thermal behaviour analysis[7,8,9].

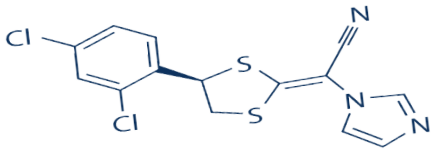

Fig. 1:Structure of luliconazole

MATERIALS AND METHODS

Materials

Luliconazole was gratis by Apex Labs Ltd, located in Chennai. Soya lecithin was procured from Vitaegen Life Science, Nagpur. Kolliphore RH 40 and Labrafil $M_2$125 CS were obtained from BASF, India. All of the chemicals utilized were of the highest possible analytical grade.

Physical identification

The obtained luliconazole sample was identified based on its physical characteristics. Colour, odour, and physical appearance were thoroughly observed.

Solubility Analysis

In three separate wide mouthed test tubes, an excess of drug was dissolved in calibrated amounts of distilled water, Methanol, Phosphate buffer solution (PBS) pH 7.4, until a saturated solution resulted. To attain equilibrium with the undissolved particles, the solution was vigorously agitated for 24 hours at a steady temperature. The solution was filtered, the filtrate was diluted with the appropriate solvents and the concentration was measured at 296 nm with the UV spectrophotometer. A triplet reading average was taken.

Saturation solubility in surfactants

Excess drugs wasdissolved in calibrated amounts of surfactants (Tween 80,Kolliphore and Labrafil) were taken for this solubility studies until a saturated solution was obtained. The solution was vigorously agitated on a rotary flask shaker for 24 hrs at a constant temperature (28±1˚c) until an equilibrium with the undissolved particles was achieved. The filtrate was diluted with the relevant solvents after the solution was filtered. These solutions were scanned in a UV spectrophotometer at 296 nm and the absorbance values were determined to estimate the solution concentration. A triplet reading was averaged.

Determination of Melting Point

The melting point was determined by using the Microcontroller based Melting Point Apparatus (Chemi Line). A capillary tube filled with Luliconazole is placed into the apparatus by accommodating the filled capillary tube inside the glass chamber containing the heating coil. When the apparatus is switched on, the heating coil works and the temperature of the glass chamber raises up. At a particular temperature the drug placed in the capillary tube melts up and this temperature was noted. The same procedure is repeated for three times in order to ascertain the precision in the measured melting point temperature.

Partition coefficient

The partition coefficient value of a drug accounts of the lipophilicity/hydrophilicity nature of the drug that can correlate the extent of permeability of the drug through the bio-membrane. Partition coefficient was determined using a separatory funnel containing a mixture of equal volume of 30 ml of each Octanol and PBS, pH 7.4. The Separatory funnel was shaken vigorously until a turbid appears. 10 mg of luliconazole was added into the turbid mixture of the separatory funnel and were shaken continuously with frequent release of pressure for 24 hrs at room temperature. The mixture was allowed to stand for 3hrs then two phases separates completely both the phases were clarified by centrifugation and the drug content dispersed in each phase was measured using a UV spectrophotometer at 296 nm. The same experimental method was repeated using a mixture of equal volumes of Octanol and water as twophase system. The Experimental runs were made in triplicate[10,11].

UV Spectrophotometric Method

Preparation of Standard Stock Solution

Standard stock solution was prepared by placing 10mg of Luliconazole into a 10ml volumetric flask and dissolving it with methanol.Standard solution was produced by pouring 2.5ml of stock solution into a 25ml volumetric flask. To make a 100µg/ml solution with potassium acetate buffer (pH-5) and distilled water, the volume was adjusted to the mark.

Preparation of working solution

A series of concentrations ranging from 4- 18 µg/ml was prepared by pipetting out 0.4, 0.6, 0.8,1. and 1.2ml of standard working stock solution to different 10 ml volumetric flasks. The UV-Visible double beam spectrophotometer was used to scan solutions between 200 and 400 nm (Shimadzu, UV-1800 spectrophotometer, Japan).

Preparation of standard graph

The standard stock solution was appropriately diluted with water to obtain a series of dilutions to contain 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 µg/ml of the drug. The absorbance of these dilutions was measured using a UV spectrophotometer at 296nm using water as blank. A graphical plot of the absorbance versus the concentration of luliconazole was constructed to yield a straight line by adopting linear regression analysis of the obtained absorbance data points. A straightline equation ($Y = mx + c$) was generated whose slope and intercept values are used to reduce the amount of the drug. [12]

Identification of drug

Luliconazole was analyzed in FTIR and the obtained IR spectrum was matched for the characteristic peaks in comparison with the reference spectrum of Luliconazole.

FTIR Compatibility studies

FTIR spectrum reveals information on the presence / absence of specific functional groups of the material studied, thereby accounts of interactions if any between the drug and other excipients. The drug, excipients such as lecithin, Labrafil, Kolliphore RH 40 and its mixtures prepared with an equimolar (1:1) ratio, were stored separately in a hermetically sealed

container and examined physically for any deleterious changes throughout a period of one month. After a month the same samples were analysed using FTIR (Shimadzu)[13,14].

Differential scanning calorimetry

A differential scanning calorimeter (DSC) was used for the thermal investigation of the luliconazole sample. The sample was heated in an aluminium pan under nitrogen conditions at a rate of 10° c/min, ranging from 0 to 800° c. The purity of the sample can be determined with the use of the DSC spectrum[15].

Results and Discussion

Physical appearance: The physical appearance of the drug was done by checking its physical identification i.e colour, odour, and appearance of the luliconazole drug. The results so obtained are discuss in below table 1.

Table1:Physical appearance of Luliconazole

Sl.no	Test	Specification	Observation
1	Colour	Pale yellow	Pale yellow
2	Odour	Odourless	Odourless
3	Appearance	Crystalline	Crystalline

Determination of solubility: The solubility of luliconazole was observed and obtained result gives highest absorbance for luliconazole in methanol. The solubility of luliconazole into different solvents was discussed in the table 2 given below:

Table2:Solubility Analysis of luliconazole

Sl.no	Solvent	Solubility
1	Distilled Water	Insoluble
2	Phosphate buffer	Slightly soluble
3	Methanol	Soluble

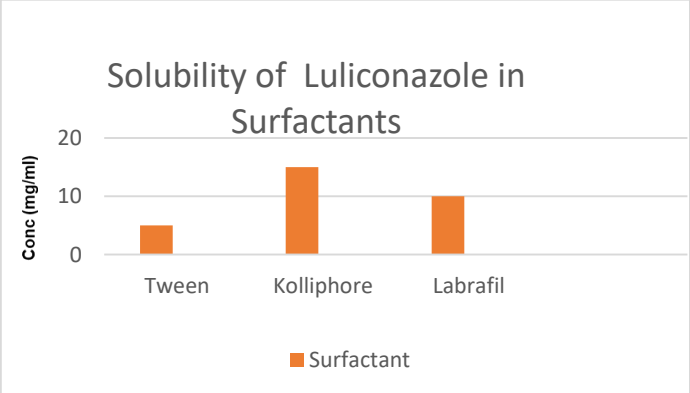

Fig.2:Solubility Analysis of luliconazole

Determination of Melting point

Melting point was obtained by mean of the three values i.e 150, 149,149.2°c. Therefore, the melting point of luliconazole was found to be148.73as shown in the table.3

Table3:Melting point for luliconazole

Melting point(°c)	Mean
150	**149.40**
149	
149.2	

Partition coefficient

The observed partition coefficient was 2.94 which exceeded the reference value of 2.86 shown in the table 4.Therefore the partition coefficient indicating that luliconazole is highly accessible for transdermal drug delivery.

Table 4: Partition coefficient for luliconazole

Standard	observed	Mean
2.86	2.90	2.94
	2.96	
	2.96	

Calibration curve

U.V. spectrophotometric Scanning of luliconazole in methanol has maximum absorbance at 296nm. The standard $\lambda_{max}$of luliconazole is shown in the fig 3.

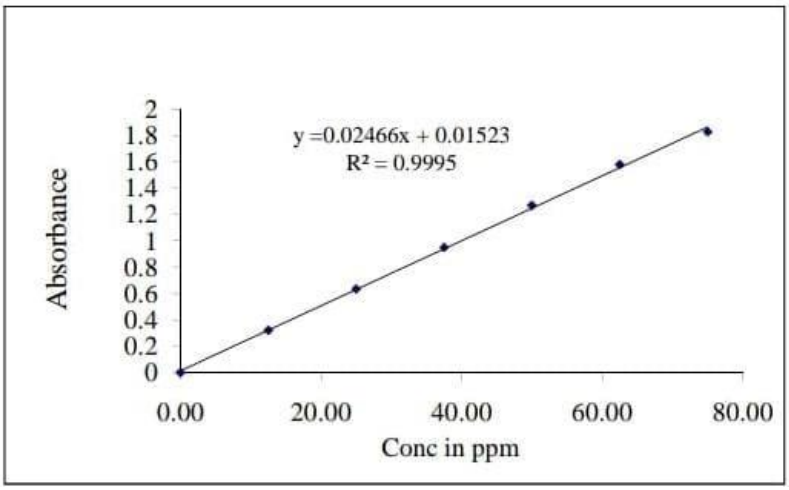

Fig.3: Standard calibaration curve of luliconazole

Table5:Calibration data of luliconazole

Sl. No	Concentration (µg/ml)	Absorbance
1	20	0.635
2	40	0.949
3	60	1.269

4	80	1.579
5	100	1.827

Correlation coefficient	0.99949
Slope	0.02466
Intercept	0.01525

The correlation coefficient (r^2) was found to be 0.9979 and the results of linearity have shown in table 5. This indicates the linear relationship between absorbance and concentration of drug.

FT-IR compatibility studies

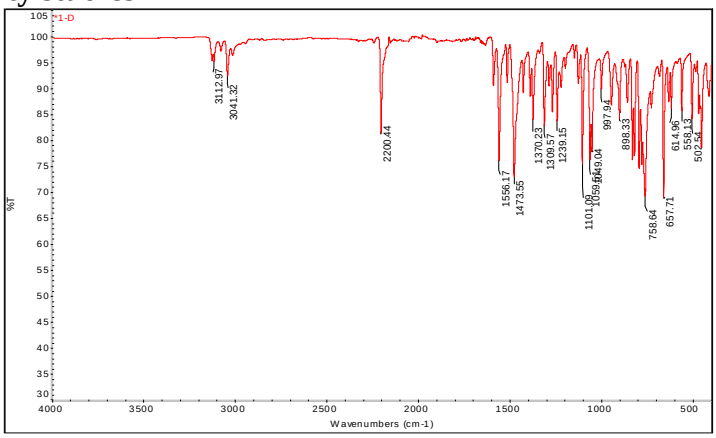

Fig. 4: FT-IR Spectrum of luliconazole

Table 6: Interpretation of FT-IR spectrum of luliconazole

Individual compound	**Functional groups**	**Characteristic peak (wave number)**
Luliconazole	C-H aromatic stretching	3112 cm^{-1}
	C=C in an aromatic ring	3041 cm^{-1}
	S-H stretching	2200 cm^{-1}

The FTIR spectrum of luliconazole showed the characteristic peak at 3112 cm^{-1} which confirmed the presence of C-H group, characteristic peak at 3041 cm^{-1} which confirmed the presence of C=C group, characteristic peak at 2200 cm^{-1} which confirmed the presence of SH group. The observed spectrum of luliconazole confirmed the purity of the Luz.

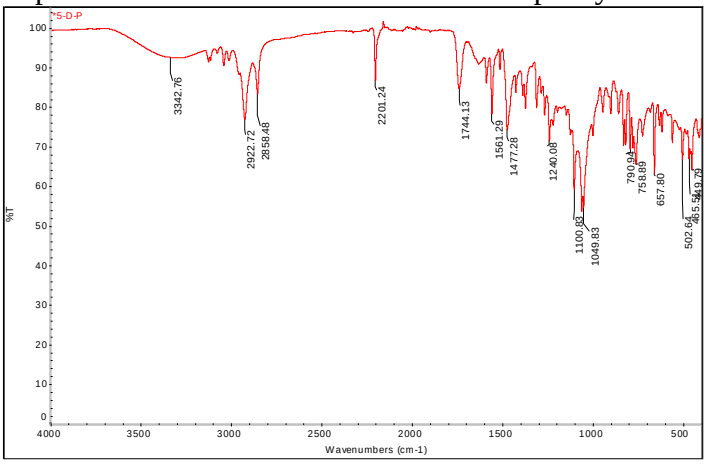

Fig.5: FT-IR Spectrum ofluliconazole with Lecithin

Table 7: Interpretation of FT-IR spectrum of luliconazole with Lecithin

Physical Mixture	Functional groups	Characteristic peak (wave number)
Luz+Lecithin	Symmetric CH_2	2854cm^{-1}
	Asymmetric CH_2	2928 cm^{-1}
	CH_3stretching	2956 cm^{-1}
	-C=O stretching	1736 cm^{-1}

The FT-IR spectrum of physical mixture of LUZ with Lecithin showed that all characteristic peaks at 2854cm^{-1}, 2928 cm^{-1},2956 cm^{-1} and 1736 cm^{-1} confirms presence ofsymmetric and asymmetric CH_2, CH_3, C=O groups respectively.Therefore the spectrum confirmed and identify the presence of functional group and purity of the drug and excipients.

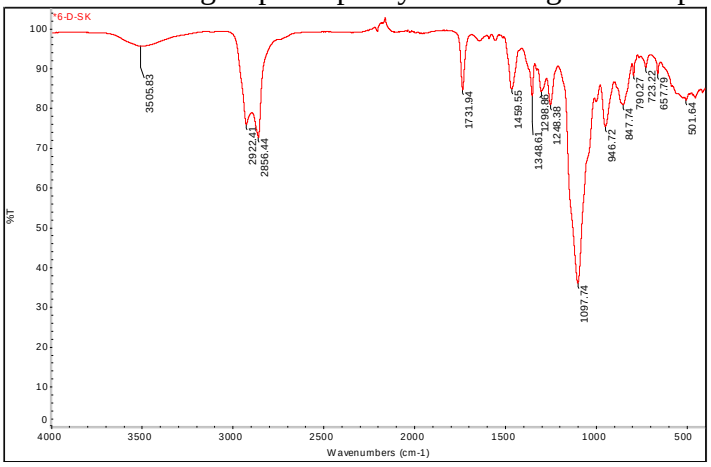

Fig. 6: FT-IR Spectrum of luliconazole with Kolliphore

Table 7: Interpretation of FT-IR spectrum of Luliconazole with Kolliphore

Physical Mixture	Functional groups	Characteristic peak (wave number)
Luz+ Kolliphore RH 40	C≡O stretch in esters	1735 cm^{-1}
	C≡C stretch in alkanes	1635 cm^{-1}
	C-H bend in alkanes	1466 cm^{-1}
	C-H rock in alkanes	1350 cm^{-1}

The FT-IR spectrum of physical mixture showed band at 1735 cm^{-1} ,1635 $cm^{-1}$for C≡O stretch,1466 cm^{-1},1350 cm^{-1} C-H bending and rocking. No difference was observed in the absorption band for chemical bonding of pure drug with excipient.

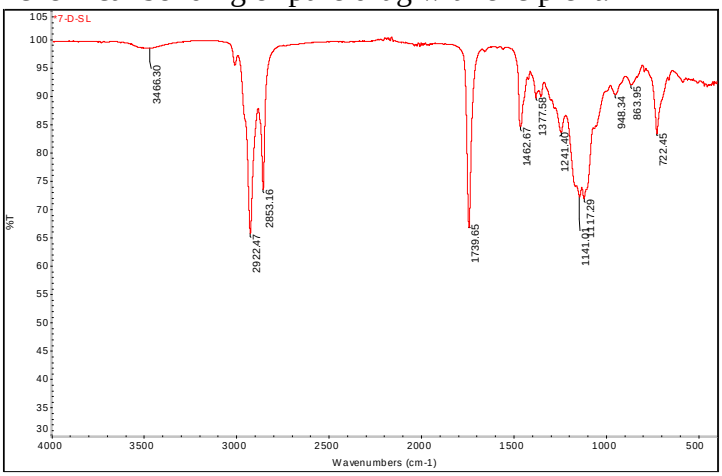

Fig. 7: FT-IR Spectrum of Luliconazole with labrafil

Table 8: Interpretation of FT-IR spectrum of luliconazole with labrafil

Physical Mixture	Functional groups	Characteristic peaks (wave number)
Luz+ Labrafil	-OH group	2916 cm^{-1}
	-CH3 group	1467 cm^{-1}
	Cyclic 5-membered ring	1734 cm^{-1}
	Aliphatic chain	1000-1200 cm^{-1}

The FT-IR spectrum of Luliconazole with Labrafil showed the characteristic peak at 2916 cm^{-1} which confirmed the presence of OH group, characteristic peak at 1467cm^{-1} which confirmed the presence of CH_3 group, characteristic peak at 1734 cm^{-1} which confirmed the presence of cyclic 5-membered ring and aliphatic chain shown the peaks in 1000-1200cm^{-1}. The observed spectrum of physical mixture confirmed the purity of the Luz with Labrafil.

Differential Scanning Calorimetry

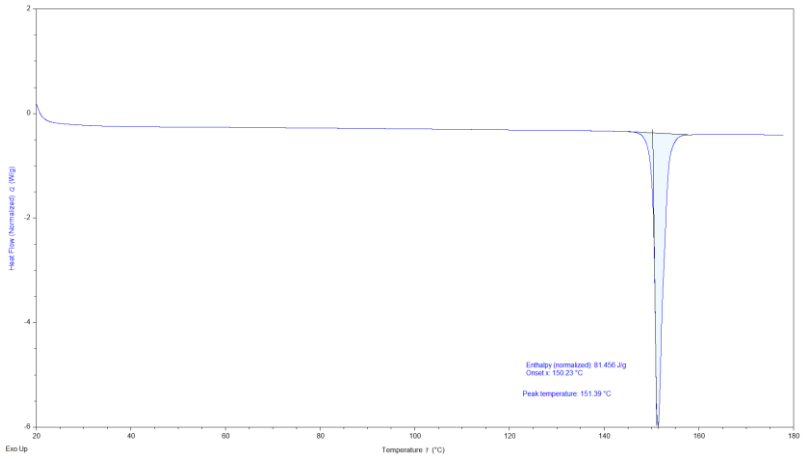

Fig. 8: DSC Thermogram of Luz

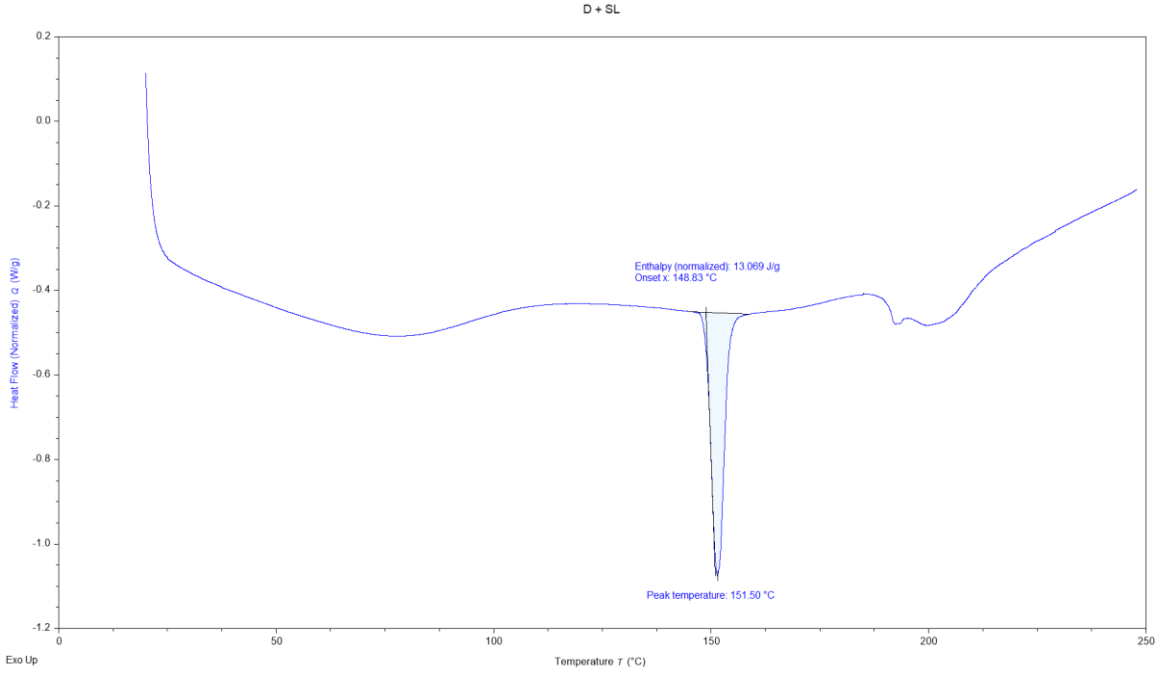

Fig. 9: DSC Thermogram of Luz with Lecithin

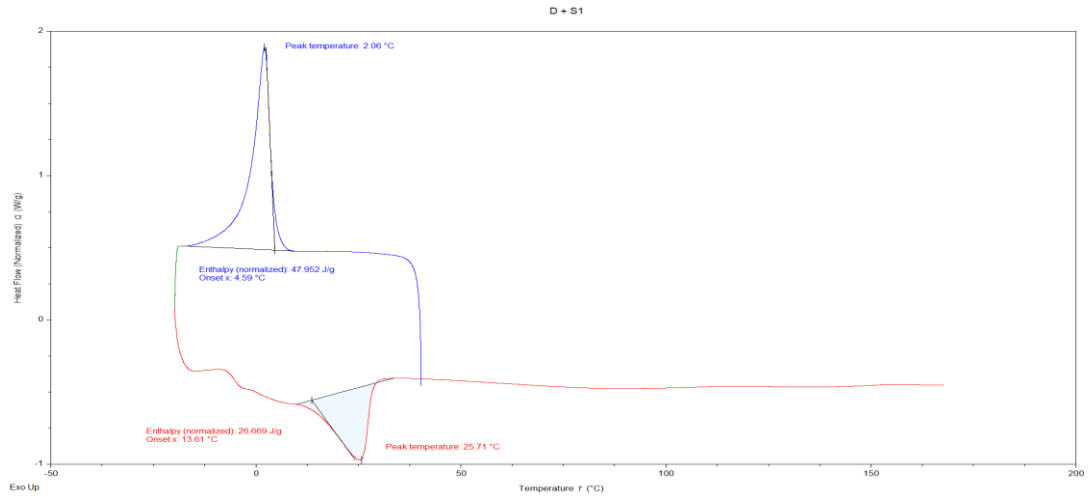

Fig. 10: DSC Thermogram of Luz withKolliphore

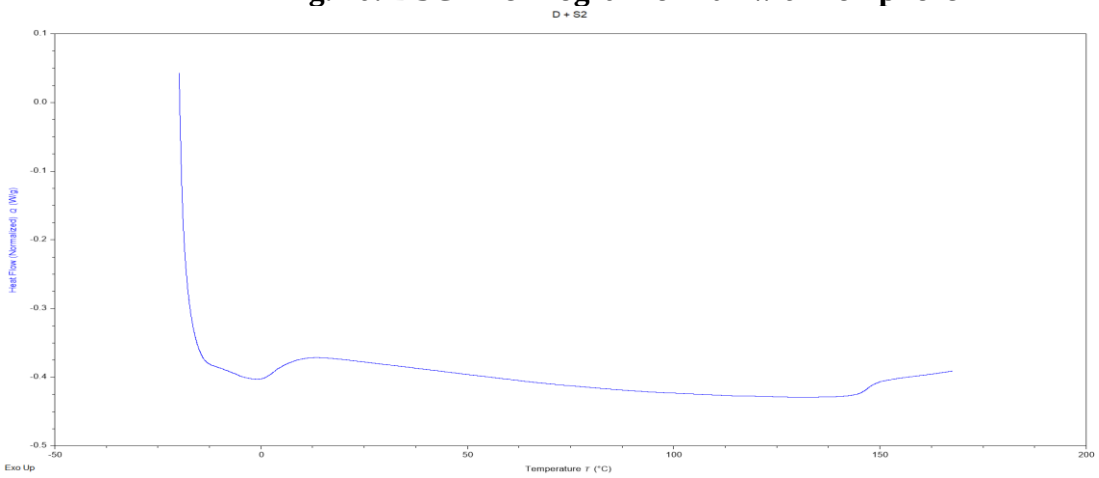

Fig.11:DSC Thermogram of Luzwith Labrafil

Table 9 : Interpretation of DSC thermogram data

Name of Component	Temperature (°c)	Heat flow (mW)
LUZ	151.39	- 1.29
LUZ+ Lecithin	212.16	-1.25
LUZ+ Kolliphore	25.71	1.29
LUZ+ Labrafil	30.12	-3.20

The thermogram of LUZ , physical mixture of drug with Lecithin ,Kolliphore and Labrafil were obtained and the melting point was found to be 151.39°C, 212.16 °C,21.71 °C, and 30.12 °C, respectively, which confirms the purity of the compounds. To investigate the possible interaction between drug and excipients , the thermograms of physical mixtures were analysed. There were no significant changes in the endothermic peak of luliconazole. Hence ,the drug was found to be compatible with the selected excipients.

Conclusion

The preformulation research on the selected drug Luz and excipients clearly investigated the viability of developing a transferosomal patches loaded antifungal Luliconazole. Preformulation tests such as solubility, melting point and partition coefficient were conducted for luliconazole to assure a sensible outcome in the development of a stable dosage form. The findings of these experimental trials were indicating that the anticipated formulation might be

successfully developed for the selected medication and excipients. Luliconazole was analysed using a UV-Spectrophotometer at 296 nm .It has been proven to be reproducible, extremely sensitive. The correlation coefficient value found for Luliconazole indicates that the proposed UV spectroscopy is based on Beer- Lambert's Law. The FTIR analysis of drugs and excipients as individual components and physical mixes in equimolar ratios was investigated. The analysis confirmed that there were no chemical interactions between Luliconazole and other excipients used including lecithin, Kolliphore RH 40 and labrafil. DSC result showed that thermogram peak was observed in all physical mixtures and there were no changes in the endothermic peak of physical mixture. As a results, the current study concludes that the chosen drug and excipients are promising for the development of a transferosomal patchesloaded antifungal designed as transdermal drug delivery system.

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