Formulation And Evaluation of Miconazole Pharmacosome by Using Solvent Evaporation Method to Enhance Solubility of Miconazole

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Abstract: This study aims to improve the solubility, bioavailability, and safety profile of miconazole through the development of a pharmacokinetic, a type of vesicular drug delivery system known for its advantages over with conventional methods. Using a solvent evaporation technique, miconazole is encapsulated in a soy lecithin-based pharmacokinetics. The pharmacokinetics obtained showed significant improvements in drug solubility, concentration uniformity and stability. One specific formulation, rated F1, with an exact ratio of miconazole to soy lecithin showed an impressive drug release rate of 94.25% within 60 minutes, in stark contrast to the release rate of only 28.90% achieved by free miconazole. This improved release profile shows the potential to improve treatment efficacy. In addition, both the standard F1 and miconazole formulations exhibited significant antifungal activity against Candida albicans, as evidenced by the minimum inhibitory concentrations (MICs) of 144.23 µg/ml and 143.31 µg/ml respectively. The innovative approach of complexing miconazole with soy lecithin through the formation of pharmacokinetics not only enhances drug solubility and bioavailability, but also contributes to minimizing potential toxic effects. These results highlight a promising pharmaceutical role as a means of improving the pharmacological properties of miconazole and other potential drugs with similar solubility challenges. This study has important implications for the development of more effective and safer therapeutic interventions in the field of antifungal therapy.

Keywords: Pharmacosomes, Miconazole, Soyalecithin, Handshake Solvent Evaporation, Bioavalability, *in-vitro* Antifungal, Solubility**.**

1. INTRODUCTION

A "pharmacosome" is a lipoidal drug delivery system where a drug (pharmakon) is joined with a carrier (soma) in a complex form. This prodrug has both hydrophilic and lipophilic characteristics, improving bioavailability by reducing interfacial tension and facilitating drug deportation through cell membranes and tissues. When exposed to water, these prodrugs assemble into one or more layers, taking into account both the surface and bulk properties of the drug-lipid conjugate [**1-2].**

Miconazole, an antifungal medication, belongs to the imidazole class. It works by inhibiting the synthesis of fungal cell membrane sterols, leading to cell damage and death. Although it is not well absorbed from the gastrointestinal tract, it is widely distributed throughout the body after administration. Approximately 20% of the dose is eliminated in the urine as inactive metabolites, indicating some degree of metabolism. Additionally, about 40% of the oral dose is excreted unchanged in the feces, suggesting significant elimination without substantial metabolism. Overall, Miconazole has limited gastrointestinal absorption but displays extensive distribution in the body, and a portion is excreted as metabolites in the urine, while a significant amount is eliminated unchanged in the feces **[3].**

Pharmacosome preparation of Miconazole aims to enhance its solubility. By formulating Miconazole into pharmacosomes, the drug's solubility can be increased. This improvement in solubility can enhance the dissolution and absorption of Miconazole, potentially improving its therapeutic effectiveness **[4].**

2. MATERIALS AND METHODS

Miconazole was received as a gift sample from BLD Pharma Gurugram, India, while soy lecithin was purchased from Purenso Global, Indore, India, both of which met analytical standards. The pharmaceutical miconazole is produced by conventional solvent evaporation, which involves the handshake technique. This approach involves evaporation of different ratios of miconazole to soy lecithin with dichloromethane as solvent over a 60°C water bath. After evaporation, the organic solvent n-hexane was incorporated, followed by filtration.

The resulting product is dried, ground and sieved through a 100 mesh sieve, ensuring uniform particle size for the final product.

3. Evaluation of miconazole pharmacosome:

3.1 Determination oF λ_{max}

To determine the maximum absorbance (λmax) of Miconazole, a stock solution of 100 mg Miconazole in 10 ml methanol was prepared and diluted with phosphate buffer (pH 6.8) to achieve the desired concentration. The resulting solution was scanned with a spectrophotometer throughout a wavelength range of 200-400 nm, and the greatest absorbance was detected at 246 nm, which was chosen for further investigation **[5].**

3.2 Establishment of Standard Curve

To create a series of serially diluted solutions of Miconazole ranging from 2-10 g/ml, 0.2, 0.4, 0.6, 0.8, and 1 ml of the stock solution were sequentially transferred into separate 100 ml volumetric flasks. Phosphate buffer (pH 6.8) was added to complete the volume in each flask. The absorbance of each diluted solution was measured at 224 nm using a spectrophotometer. A calibration curve was then constructed by plotting the absorbance values on the y-axis against the corresponding concentrations (g/ml) on the x-axis to establish the relationship between absorbance and concentration **[6].**

3.3 Drug Content Determination

50 mg of Miconazole was weighed and transferred to a volumetric flask to determine the amount of medication in Miconazole pharmacosomes. To ensure appropriate mixing and dissolution of the complex, 100 ml of pH 7.4 phosphate buffer was added to the flask and swirled for 24 hours. Following the stirring period, appropriate dilutions were generated, and the drug content in the diluted solution was determined using UV spectrophotometry at 246 nm. The medication content in Miconazole pharmacosomes was precisely determined using this approach **[7].**

3.4 Determination of Solubility

To assess the apparent solubility of Miconazole and its pharmacosomes, excess amounts of both were mixed with distilled water, pH 6.8 phosphate buffer, and n-octanol in sealed vials. After shaking for 24 hours at 25°C, the saturated solutions were centrifuged, and the supernatant was filtered and diluted. Spectrophotometric analysis at 246 nm was performed to quantify the solubility of Miconazole and its pharmacosomes. By comparing their solubilities, the change caused by complexation was determined **[8].**

3.5 Dissolution Studies

Miconazole capsule dissolution was tested using the basket apparatus (USP XXIV dissolution test apparatus Type I) at 37°C 0.5°C, with stirring at 75 rpm. For 10 hours, the capsules were submerged in a pH 6.8 phosphate buffer solution (900 ml) as the extraction solvent. 10 mL of the solution was collected and replaced with fresh buffer solution at regular intervals. A double-beam spectrophotometer was used to measure the absorbance of the samples at 246 nm. The cumulative release of the medication was calculated using a standard curve and related equations.

3.6 Fourier Transform Infrared Spectroscopy (FTIR)

To validate the production of the drug and distinguish it from its individual components or physical combination, infrared spectroscopy (IR) using FTIR (Bruker, Tensor 27) was performed at the Central Instrument Lab in Bhatinda, Punjab. This analysis aimed to identify unique characteristics in the drug's spectrum resulting from chemical interactions between the drug and the phospholipid. The formation of new bonds during these interactions leads to spectral differences between the drug and its separate components or physical combination. By comparing the IR spectra of the drug with those of its individual components and physical combination, the presence of new bonds can be detected, confirming the production of the drug **[9].**

3.7 Differential Scanning Calorimetry (DSC)

The DSC at Jan Nayak CH. Devi Lal Memorial College of Pharmacy in Sirsa was used for thermal analysis on pure drugs and excipients to identify potential incompatibilities. Variations and shifts in melting endotherms, exotherms, and reactive enthalpies were observed. DSC analysis was conducted in a nitrogen environment, with a temperature range of 50 °C to 300 °C and a consistent temperature increase of 10 °C per minute. Monitoring the thermograms allowed for a quick assessment of potential incompatibilities, providing valuable insights for optimized drug formulations **[10].**

3.8 Scanning Electron Microscopy (SEM)

The surface shape of the pharmacosomes was investigated using Scanning Electron Microscopy (SEM) with a Carl Zeiss Merlin Compact SEM. The SEM provided high-resolution imaging of the pharmacosomes' surface topography, aiding in understanding their physical characteristics and potential applications in drug delivery **[11].**

3.9 *In vitro* Antifungal Activity

Antifungal effect of Formulation in Comparison with Miconazole Against *Candida albicans* MTCC 183. These pathogenic strains were obtained from the Microbial Type Culture Collection, IMTECH, Chandigarh, India. Antifungal activity assessed using disc diffusion technique. Fungal pathogens inoculated on agar plates. Filter paper discs (4 mm) impregnated with test formulation and Miconazole. Plates incubated at 30°C for 32 hours. Zones of inhibition measured in millimeters to determine antifungal activity.

In this study, microorganism cultures were preserved in Sabouraud dextrose agar, while fungal pathogens were maintained in Sabouraud dextrose broth. Antifungal activity was assessed using the disc diffusion technique with Whatman No.1 filter paper impregnated with test formulations and standard Miconazole. Inhibition zones were measured after incubation at 30°C for 32 hours **[12]**

The antifungal efficacy of the formulation and Miconazole was compared to a negative control using the filter paper disc diffusion method. The zone of inhibition in millimeters indicated antifungal activity. The inhibition zone of the test sample (formulation) was divided by the inhibition zone of the standard drug (Miconazole) to compute the activity index. The activity index measures the relative effectiveness of the plant extract (formulation) compared to the standard drug in inhibiting fungal growth.

4. RESULTS AND DISCUSSIONS

4.1 Calibration Curve of Miconazole

By analysing the solution along the wavelength range of 200-400 nm, the concentration of pure Miconazole medication at its maximum wavelength (max) was calculated. Through this analysis, it was observed that the maximum wavelength for Miconazole was 246 nm. For the calibration curve of Miconazole, the drug was dissolved in phosphate buffer with a pH of 6.8. The curve was constructed using a concentration range of 2–10 µg/ml, and it exhibited linearity with a high regression coefficient (R2) of 0.986 as shown in Table 1 and figA.

Table : 1 Calibration Curve Data of Miconazole

Concentration (µg/ml)	Absorbance
0	0
2	0.234
4	0.367
6	0.483
8	0.643
10	0.761

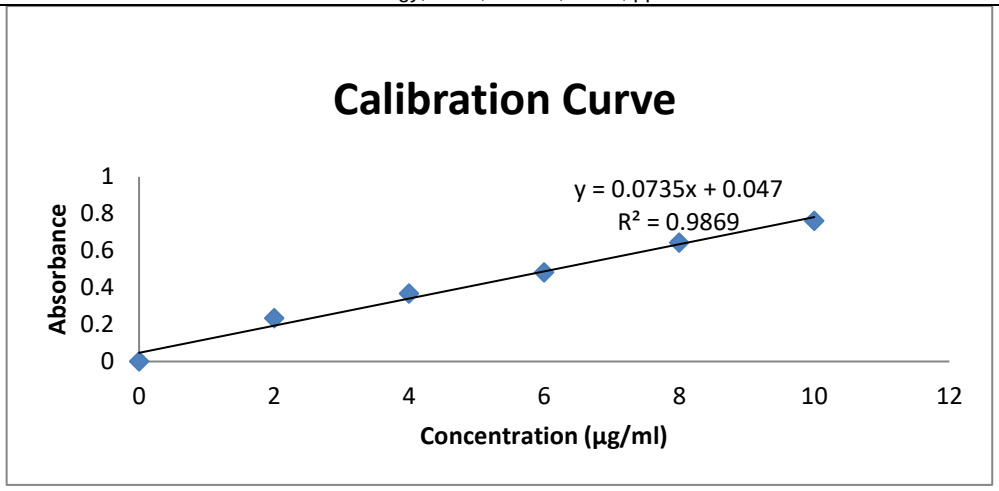

Fig A: Calibration curve of Miconazole

4.2 Compatibility Studies

After analyzing and composing the infrared (IR) spectra of the combined combination of the excipient, soya lecithin, and the pure drug Miconazole, as well as the spectra of the drug's combination with soya lecithin and Miconazole pharmacosomes . Observations found that the combined spectra of the medicine and excipient contained all of Miconazole's distinctive peaks[Table2]. As their spectra overlap without major changes, this shows that there are no compatibility difficulties between the medicine and the excipient. Fig B,C,D shows IR spectra of Miconazole , soy lecithin and Miconazole; soy lectin physical mixture respectively.

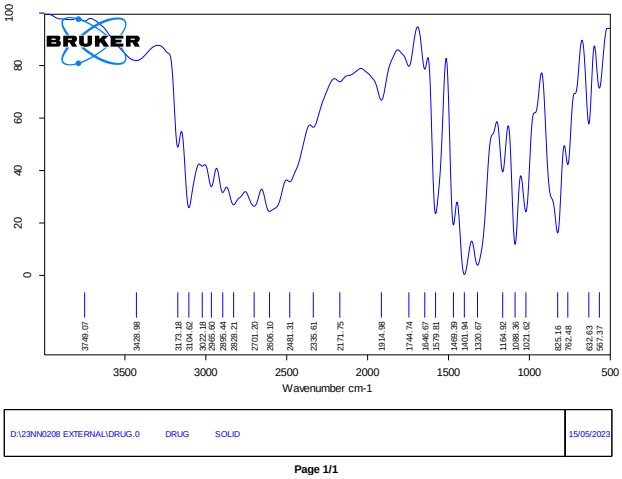

Fig B: IR spectrum of Miconazole pure drug

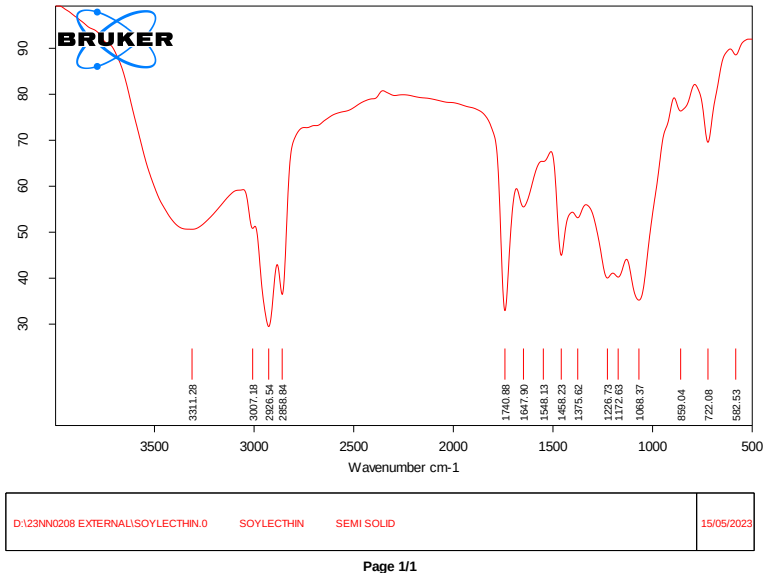

Fig C: IR spectrum of Soya Lecthin

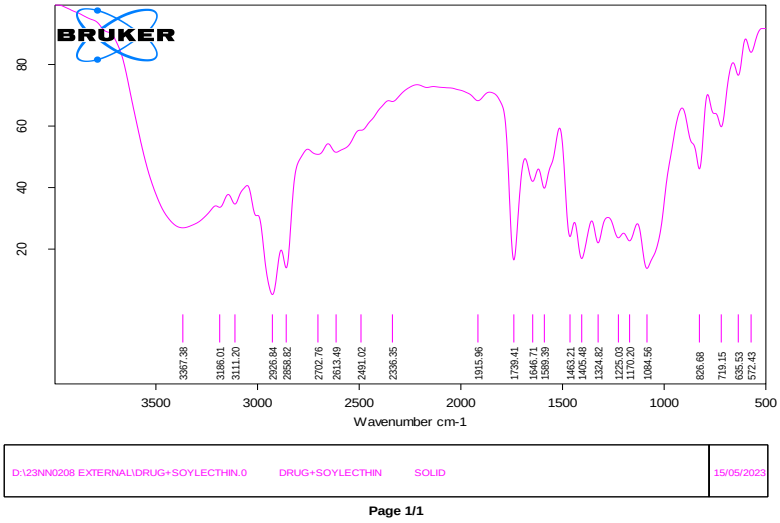

Fig D: IR spectrum of Miconazole+Soy Lecthin

Table 2: Characteristics peak of Miconazole , Soya Lecithin and their physical mixture

Specification	Wavenumber cm^{-1}		
	Miconazole	**Soya lecthin**	**Micnozole+Soyalecthin**
C-H stretching	2895.44	2858.84	2858.82
N-H stretching	3428.99	3311.28	3367.38
C=O stretching	1744.74	1740.88	1739.11
C=C stretching	1646.67	1647.90	1648.71
C-Cl stretching	825.16	_	826.68
C-O-C stretching	1164.92	1172.63	1170.20

4.3 Drug Content Studies

The quantity of Miconazole present in the pharmacosomes was determined using UV spectrophotometry at a wavelength of 246 nm, in phosphate buffer (pH 6.8). Drug content analysis of Miconazole pharmacosomes revealed that the complex contained between 89.40 and 97.51 percent of the drug. These findings indicate that the formulations have an appropriate drug content.

One significant advantage of pharmacosomes over liposomes is the high drug loading capacity. As the lipid content increased in the formulations, the proportion of drug loading decreased[Tble 3]. Among the tested formulations, Formulation F1 exhibited the highest drug content, with a level of 97.51 percent**.**This high drug loading capability of pharmacosomes is beneficial, as it allows for the efficient delivery of a larger amount of the drug, potentially enhancing therapeutic efficacy.

Table 3: Results of Drug Content Studies

Formulation	Drug Content (% w/w)
F1	97.51
F2	97.20
F3	94.41
F4	94.30
F5	91.53
F6	91.00
F7	89.40

4.4 Solubility Studies

Miconazole's solubility was tested in a variety of solvents, including water, pH 6.8 phosphate buffer, and methanol[Table 4]. The change in solubility caused by complexation was measured using UV spectrophotometry at a wavelength of 246 nm. Miconazole pharmacosomes had much better solubility than the pure medication, according to the findings. Miconazole's increased solubility in pharmacosomes can be attributed to two key factors: the solubilization theory and the complex's amorphous form. Micelle production in the medium, as well as the complex's amorphous structure, contribute to Miconazole's improved solubility.

Table: 4 Solubility profile in different media

Formulation	Water (mg/ml)	pH 6.8 Phosphate Buffer (mg/ml)	Methanol (mg/ml)
Pure drug	0.03	0.115	0.85
F1	0.779	5.275	5.967
F2	0.765	5.132	5.433
F3	0.642	4.760	5.115
F4	0.684	3.870	4.230
F5	0.537	3.650	4.112
F6	0.543	3.765	4.248
F7	0.627	4.357	4.598

The presence of phospholipids in pharmacosomes acts as amphiphilic surfactants, thereby enhancing the drug's solubility through wetting and dispersion capabilities.

Among the tested formulations, Formulation F1 displayed the highest solubility of Miconazole. This suggests that the specific composition of F1, including the type and proportion of phospholipids utilized, optimized the drug's solubility in the pharmacosomes. The increased solubility of Miconazole in pharmacosomes has several advantages. It can enhance the drug's bioavailability, allowing for better absorption and distribution in the body. This, in turn, can potentially improve the drug's therapeutic effectiveness.

4.5 *In-Vitro* Dissolution Studies

A 60-minute *in-vitro* release study was conducted on all formulations using the USP XXIV Type I dissolving test device, specifically employing the basket apparatus. Percentage cumulative drug release over time was calculated and plotted to assess the drug release profile[Fig E]. The Miconazole pharmacosomes exhibited a superior solubility profile compared to the pure drug. The formulations demonstrated a cumulative drug release ranging from 78.50% to 94.25%, whereas the pure drug had a significantly lower release of only 28.90% after 1 hour. At a drug to soya lecithin ratio of 1:1, Formulation F1 exhibited the most significant drug release after six minutes. The presence of phospholipids in the pharmacosomes contributed to their improved dissolution profile by enhancing drug solubility through wetting and dispersion capabilities. Table 5 indicates *In-vitro* drug release of Miconazole pharmacosomes. Several factors, including particle size, crystal morphology, surface area, surface energy, and wettability, influence the intricate process of solid dispersion. Phospholipids, being amphiphilic surfactants, possess wetting and dispersion properties that enhance the dissolution profile of the complex by improving the drug's solubility.

Table 5: Cumulative Drug Release vs Time

Time (min)	Pure Drug CDR %	F1 CDR %	F2 CDR %	F3 CDR %	F4 CDR %	F5 CDR %	F6 CDR %	F7 CDR %
5	1.48	3.75	2.45	1.92	1.99	2.33	2.54	2.34
10	2.57	10.50	9.42	8.80	7.54	8.45	7.58	5.55
15	4.24	20.65	17.22	15.89	13.31	14.37	13.60	12.25
20	7.35	33.65	26.58	24.56	19.41	22.64	22.20	17.85
25	10.12	39.54	37.65	33.47	32.24	40.25	28.25	28.25
30	13.95	52.10	45.78	41.99	39.23	46.34	40.64	31.49
35	16.34	57.65	52.35	47.77	44.57	49.58	48.00	44.81
40	18.88	64.75	58.43	51.67	45.89	51.35	49.67	52.26
45	20.78	72.83	63.85	56.96	50.72	55.76	52.59	53.50
50	22.64	83.44	70.56	61.64	59.05	61.50	62.61	58.45
55	25.25	89.55	81.73	70.25	73.84	73.56	71.15	72.40
60	28.90	94.25	89.26	84.20	82.50	83.34	82.45	78.50

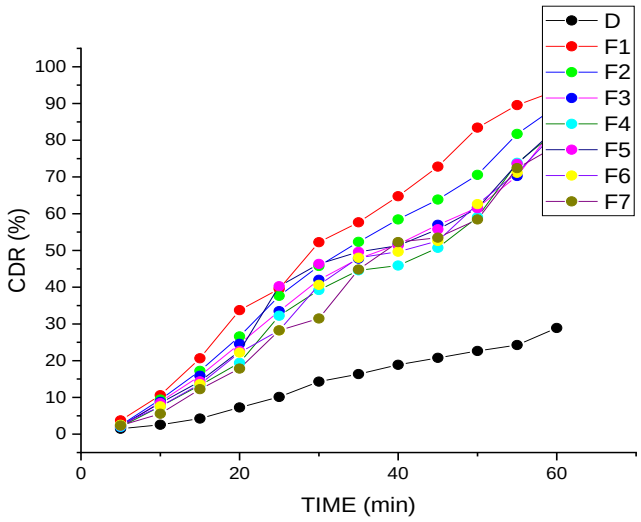

Fig E: *In- Vitro* drug release of Miconazole pharmacosome

4.6 Fourier Transform of Infrared Spectroscopy

The spectra obtained from the formulation were compared with the standard peaks listed in table 6 and as shown in Fig F. It was observed that there were no significant differences between the standard and formulation peaks. No new peaks were observed, and there was no overlapping or substantial shifting in the functional group peaks. These findings indicate the stability of the drug during the complexation process.

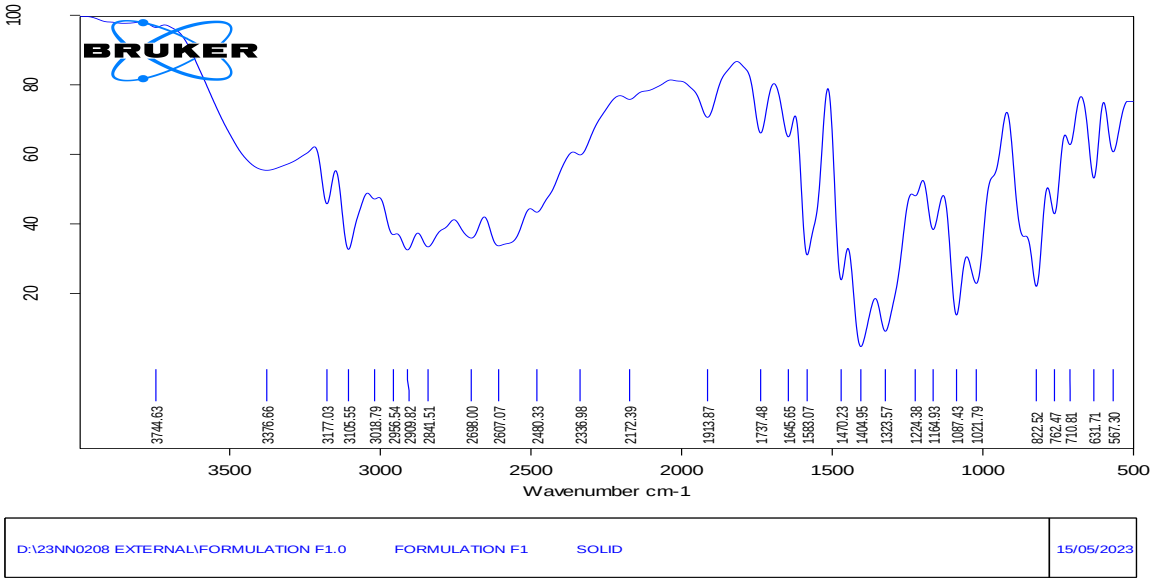

Fig F: FTIR Spectrum of Miconazole Pharmacosomes

Table 6 Characteristic Peak of Formulation and Miconazole

Specification	Miconazole	Formulation Wave Number (cm^{-1})
C-HStretching	2895.44	2841.51
N-H Stretching	3428.99	3376.66
C=O Stretching	1744.74	1737.48
C=CStretching	1646.67	1645.85
C-Cl Stretching	825.16	822.52
C-O-C Stretching	1164.92	1164.93

4.7 Differential Scanning Calorimetry

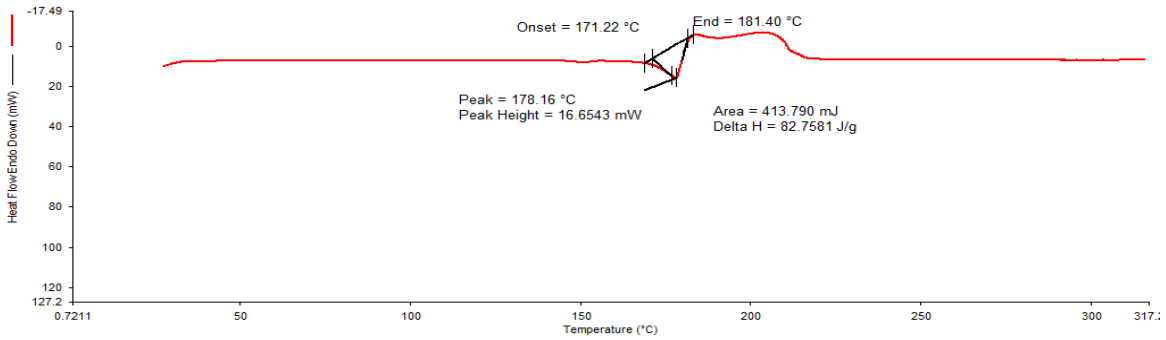

Fig G: DSC curve of Miconazole

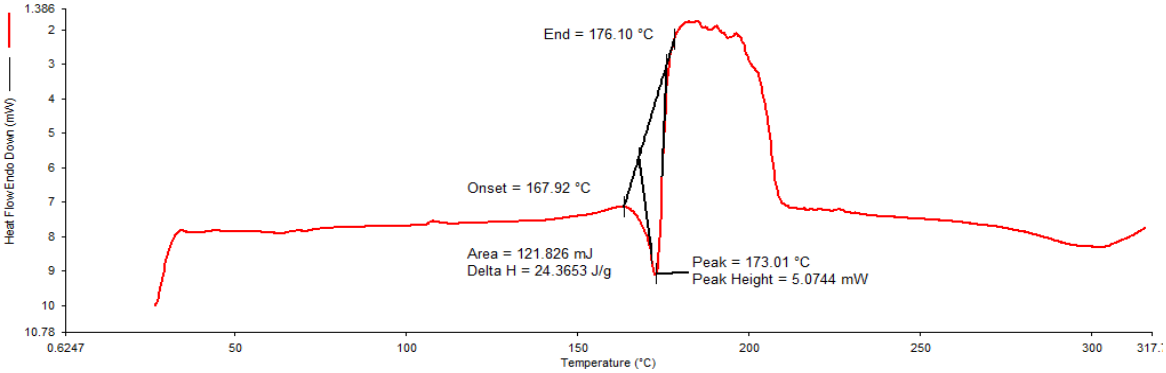

Fig H: DSC curve of Miconazole pharmacosome

The DSC thermograms of DRUG exhibit 2 endotherm at 171.22°C (onset) and 181.40°C (end point). Weather the same endotherm (171.22°C) signifies the release of bound water molecules while endothermic peak at 181.40°C which corresponded to its melting point (Fig G) and the DSC thermograms of formulation found to exhibit endotherm at 176.10°C (Fig H). These curves show that the peaks are nearly same so the drug was present in the formulation.

4.8 Scanning Electron Microscopy

The utilization of SEM was employed to analyze the physical structure of the particles. The SEM image clearly displayed that the pharmacosomes had a rod-like shape. It is important to note that the diverse levels of purity in the phospholipids, which are inherent constituents, can lead to the formation of products exhibiting different morphologies. The size of pharmacosome obtained 2um as shown in Fig I.

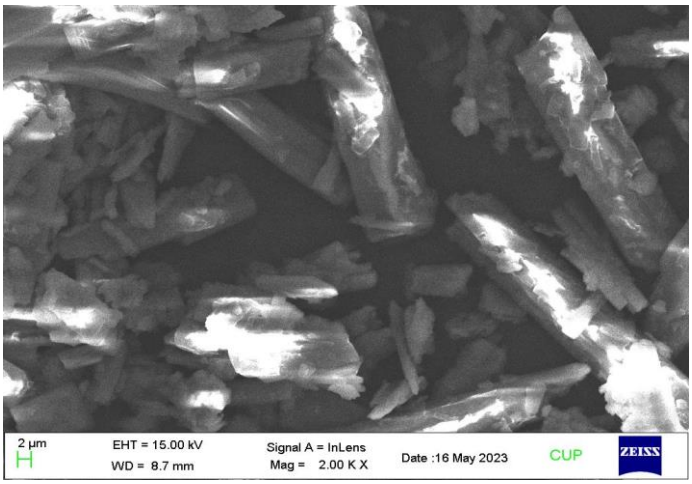

Fig I: Scanning Electron Microscopy

4.9 *In –Vitro* Antifunagal activity:-

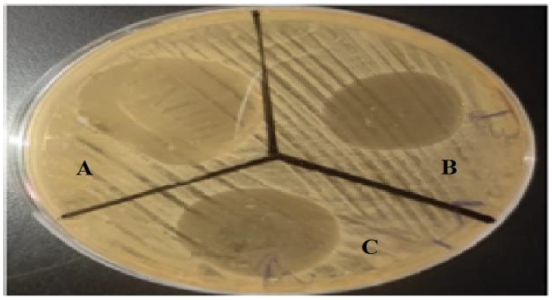

Fig J: Antifungal efficiency of Formulation (B) and standard Miconazole (C) in comparision to negative control (A) by disk diffusion assay method

The MICs of Formulation (B) and standard Miconazole (C) in comparision to negative control (A). Formulation (B) and standard Miconazole (C) exhibited antifungal activity against *Candida albicans* with MICs of 144.23 and 143.31 µg/ml, respectively (Figure J & Table 7).

Table 7: Antifungal efficiency of Formulation (B) and standard Miconazole (C) in comparision to negative control (A) by disk diffusion assay.

S. No.	Microorganism	Control	Zone of inhibition (mm)	
			Formulation	Miconazole
1.	Candida albicans	0	23	21

The zone of inhibition of formulation (B) and pure drug Miconazole (C) is 23 and 21 respectively. The formulation exhibit more zone of inhibition than the pure drug that means formulation work more on fungal strain *Candida alibicans* than the pure drug. The formulation increases the solubility of drug that's why it inhibits fungal growth more than that of pure drug.

CONCLUSION

Pharmacosomes were developed to enhance the solubility, bioavailability, and safety of Miconazole, an antifungal drug. Miconazole was complexed with soya lecithin using a solvent evaporation method. The resulting pharmacosomes were comprehensively evaluated for quality, solubility, stability, morphology, dissolution, and antifungal activity. The complex showed improved solubility, potentially reducing toxicity. Formulation F1 had high drug content (97.51% w/w), showed rod-shaped pharmacosomes, and demonstrated superior drug release (94.25%) compared to free Miconazole (28.90%) after 60 minutes. Formulation (B) exhibited antifungal activity against Candida albicans with MICs of 144.23 µg/ml and a 23mm inhibition zone. The complexation improved solubility, bioavailability, and antifungal activity.

Future prospects include further in-vivo studies to assess the clinical applicability of the optimized pharmacosome formulation (F1) in treating fungal infections. Additionally, investigating the long-term stability, scalability, and potential for targeted delivery of these pharmacosomes could open new avenues for enhancing drug efficacy and reducing side effects. Furthermore, the promising formulation F1 serves as a versatile platform, forming the basis for various forms of formulations such as tablets, capsules, creams, ointments, lotions, and more. This adaptability could allow for tailored administration routes and improved patient compliance. Exploring the versatility of the pharmacosome approach in improving other poorly soluble drugs' performance may contribute to advancing drug delivery strategies. Continued research in this direction could revolutionize the treatment of various medical conditions and improve patient outcomes.

Author's Statement

We, Hanumant Alias Abhishek Garg, Reena Sheoran, Neelam Pawar,Sanjeev and Rahul hereby declare that the work presented in the research paper titled "Pharmaceutical formulation and evaluation of Miconazole using solvent evaporation to improve the solubility dissolution of Miconazole" is the result of our initial study conducted at Pharmaceutical Sciences, Chaudhary Bansi Lal University, Bhiwani, Haryana, India.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could affect the work reported in this article.

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Abbreviations

MICs: Minimum Inhibitory Concentrations

µg/ml: Micro gram per milli litter

mg: milli gram

ml: milli liter

°C: Degree Celsius

nm: nano meter

g/ml: gram per milli litter

USP: Unitied State Pharmacopeia

Rpm: rounds per minute

cm-^{1}: Centi meter inverse

mg/ml: milli gram per milli litter

CDR: Cumulative Drug Release

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