Research Article

Cuestiones de Fisioterapia

Pharmaceutics

FORMULATION AND EVALUATION OF MICONAZOLE NITRATE–LOADED TRANSFEROSOMES INCORPORATED INTO TRANSDERMAL PATCHES FOR ENHANCED ANTIFUNGAL DELIVERY

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Abstract

Background: Transdermal delivery of antifungal agents experiences ongoing difficulties because the stratum corneum functions as an effective protective barrier. Transferosomes function as ultra-deformable lipid vesicles which contain phospholipids and edge activators to provide improved skin penetration capabilities and continuous medication release. Objective: Todevelope transferosomes which contained miconazole nitrate to achieve better antifungal treatment through controlled administration methods which is then tested on polymeric transdermal patches. Methods: Transferosomes are createdby using thethin-film hydration methodwhich contained various soy lecithin and surfactant (Span 20 and Span 60) ratios. The researchers assessed the vesicles through testing their particle size and SEM-based morphological analysis and their ability to trap materials. The transdermal patchescombined PVP K-30 and HPMC K4M and propylene glycol as a plasticizer with the optimized transferosomal dispersion. It ismodified by Franz diffusion cell system to test prepared patches for their drug diffusion abilities and their physicochemical characteristics. Results: The enhanced formulation (F4) achieved its highest entrapment efficiency with a successful rate of 50.6 ± 1.0% and generated particles that measured 460 nanometers. SEM analysis confirmed the existence of spherical vesicles that exhibited a smooth appearance. The patches which contained transferosomes showed uniformity in their thickness which ranged from 0.91 to 0.95 millimeters and their drug content which ranged from 92 to 95% and their moisture content. The F1 formulation released 86.78% of its contents through in-vitro diffusion tests which showed sustained drug release for 10 hours. Conclusion: The transdermal patches that contained transferosome technology showed significant improvement of miconazole nitrate drug delivery and continuous release capabilities which made them suitable for use as an effective antifungal transdermal delivery system.

Keywords: Transferosomes, Miconazole nitrate, Transdermal patch

Introduction

Fungal infections that affect both skin and mucous membranes represent a major dermatological problem across the world. [1]Superficial fungal infections become more common in tropical and humid environments because these conditions create an ideal environment for fungal growth which leads to skin discomfort and inflammation and multiple skin infections. [2]Miconazolenitratean imidazole derivative

prevents fungi from developing ergosterol which results in fungal cell membrane destruction and increased cell membrane permeability. [3]

Miconazole nitrate demonstrates effective antifungal properties against multiple types of fungi, but its topical application through creams and ointments presents a main challenge which prevents the drug from effectively reaching the stratum corneum to achieve transdermal delivery. [4]The drug presents restricted permeability, which forces patients to take larger doses with more frequent use, but this practice leads to local discomfort while it decreases patient adherence.[5]

Transfersomes which are ultra-deformable lipid vesicles result from the combination of phospholipids with edge activators. The organisms have the ability to move through openings which are smaller than their body size because of their flexible bilayer structure. The vesicles acquire their flexible properties through surfactants which allow them to move through the skin's intercellular lipid matrix. [6]Transferosome transdermal patches provide enhanced skin penetration which allows drugs to be released over an extended period. The present study aimed to develop and evaluate miconazole nitrate transdermal patches which contained transferosomes while investigating their physicochemical properties and in-vitro diffusion characteristics. [7]

EXPERIMENTAL SECTION

Materials

A gift sample of miconazole nitrate was acquired from a reputable pharmaceutical producer. S.D. Fine Chemicals Ltd. in India sold us cholesterol and soybean phosphatidylcholine. Loba Chemie Pvt. Ltd. in Mumbai supplied us with Brij-35 and Span 80 and sodium cholate. The approved vendors supplied all the polymers which we used to create patches that included hydroxypropyl methylcellulose (HPMC K15) as one of their components.

Potassium dihydrogen phosphate and disodium hydrogen phosphate and ethanol and methanol and chloroform as analytical grade reagents which they received in their original form are used. A dialysis membrane from Himedia Laboratories in Mumbai which has a molecular weight cut-off of 12,000 Da and the research required fresh double-distilled water are used throughout the entire study.

Preformulation Studies

Determination of λmax

Miconazole nitrate was produced as a stock solution in phosphate buffer with a pH of 7.4. The solution was tested with a double beam UV-visible spectrophotometer which scanned between 200 and 400 nanometers to determine the maximum absorption wavelength (λmax) of the solution.

Preparation of Standard Calibration Curve

Theprimary stock solution was prepared by dissolving a specific weight of miconazole nitrate in phosphate buffer which had a pH of 7.4.

The concentrations between 5 and 25 µg/ml is achieved through the process of serial dilutions. The absorbance of each solution at its specific λmax before they created a calibration curve by plotting concentration against absorbance.

Drug–Excipient Compatibility Studies

Compatibility tests used Fourier Transform Infrared (FT-IR) spectroscopy as their testing method. The

hydraulic press crushed the pure drug and physical drug mixes which contained phospholipids and excipients into pellets after the materials had been ground with potassium bromide. The 4000–400 cm^{-1} range was used to scan the pellets. The spectra examination detected important changes which resulted in the disappearance of specific peaks.

Preparation of Miconazole Nitrate–Loaded Transfersomes

The transfersomes were created through the application of the thin film hydration technique. They used a round-bottom flask to create a solution which contained chloroform and methanol and ethanol to dissolve precise amounts of soybean phosphatidylcholine and cholesterol and edge activators which included Span 80 and sodium cholate and Brij-35 at different molar ratios.

The organic solvents were removed from the flask through the rotary evaporator which operated at reduced pressure to create a thin lipid film that formed on the inner surface of the flask. And further drying of the lipid film to eliminate all remaining solvent. Phosphate buffer solution dissolves miconazole nitrate to hydrate the dry film through controlled rotation at a specific speed.

It is hydrated until multilamellar vesicles started to form. The uniform nanosized transfersomes is obtained through sonication of the vesicular dispersion which also reduced the size of the vesicles. The prepared dispersion was stored at 4°C until further evaluation.

Table 1: Composition of Miconazole nitrate transferosomes

Formulation code	Surfactant	PC: Surfactant	Chloroform: Methanol	Miconazolenitrate (mg)
F1	Span 20	1:1	6:4	1
F2	Span 20	1:2	6:4	1
F3	Span 60	1:1	6:4	1
F4	Span 60	1:2	6:4	1

Evaluation of Transfersomal Formulations

Morphological Study

Theoptical microscopy is used to study the vesicular structure of the sample. The tested vesicle formation by applying a small amount of transfersomal dispersion on a glass slide which they examined through the correct magnification.

Table 2: Morphological studies of miconazole nitrate

Properties	Reported	Observed
Appearance	White crystalline powder	White crystalline powder
Odour	Odourless	Odourless
Melting point(^{0}C)	179-182^{o}C	180^{o}C ±1.52
Solubility in Methanol	13mg/ml	11mg/ml
Solubility in Propylene glycol	43 mg/ml	42mg/ml

Identification (UV)	272nm	272nm

Particle Size Analysis

The vesicle size distribution was determined through the use of a laser diffraction particle size analyzer. The sample required proper dilution with distilled water before measurements because multiple scattering effects needed to be avoided.

Zeta Potential Measurement

The zeta potential of the vesicles was measured using a zeta sizer instrument to determine their stability and surface charge characteristics. The samples required dilution with distilled water before their analysis could begin.

Entrapment Efficiency

The entrapment efficiency was determined through the centrifugation process which separated free drugs from entrapped drugs in the transfersomal dispersion. The drug-free supernatant is collected to conduct spectrophotometric analysis. Total drug measurements and free drug measurements is used to determine the quantity of drug that was contained within the vesicles.

In-Vitro Drug Release Study of Transfersomes

Dialysis membrane diffusion to examine the medication release in their laboratory experiments. It used dialysis membrane which had been soaked in receptor media before its application. Andexperimented by placing a specific quantity of transfersomal dispersion inside a dialysis bag which they then submerged in phosphate buffer maintained at pH 7.4 and 37 ± 0.5°C while continuously stirring the solution. The samples are collected at scheduled times then used spectrophotometric methods to analyze them.

Preparation of Transfersome-Loaded Transdermal Patches

Solvent casting is used to create transdermal patches which contained their enhanced transfersomal formulation. The uniform polymer solution is achieved by dissolving the required polymer amounts in the correct solvent system. The plasticizer functioned to enhance the material's flexibility. The transfersomal dispersion was added to the polymeric solution through constant stirring until complete dispersion was achieved. A glass flat moldused to dry their mixture until all solvents had evaporated under controlled temperature conditions. Thepatches are peeled of before cutting them into equal parts to evaluate their properties.

Table 3: Composition of Transferosome-Loaded Transdermal Patches

Formulation code	Concentration of PVPK-30 (mg)	Concentration of HPMC K4M (mg)	Concentration of Plasticizer (%)	Volume of solvent (ml)
F1	200	300	10	10
F2	200	300	20	10
F3	200	300	30	10

Evaluation of Transferosome-Loaded Transdermal Patches

Physical Appearance

A visual examination of the organoleptic and physical characteristics of the developed transfersome-loaded transdermal patches is performed. Theassessment of each patch to determine its surface uniformity and its ability to maintain smoothness and flexibility and its transparency and ability to show drug crystals and cracks and air bubbles under normal daylight conditions.

The surface roughness measurements is used to confirm that transfersomes were distributed evenly throughout the polymeric matrix. The visual inspection process confirms that the solvent casting technique produced films which contain no defects and meet the requirements for topical application.

Thickness Measurement

A digital micrometer screw gauge that had been calibrated was used to measure the thickness of the produced patches. The measurements are conducted at three different locations on each patch which included the center and two outer regions. The average thickness calculationsisused to determine the film casting consistency. The patch requires uniform thickness to achieve consistent drug distribution and to maintain predictable drug release patterns across its entire surface area.

Weight Uniformity

The weight fluctuation experimentsis performed by weighing each selected patch through an analytical scale. It requires all patches to undergo trimming until they reached their standardized size before conducting weight measurements.

The polymeric film production measures consistency through the calculation of average weight and standard deviation. The consistent weight measurement confirms that the polymer and entrapped transfersomes distribute evenly throughout the matrix.

Folding Endurance

Folding endurance testing revealed the mechanical strength and flexibility of transdermal patches. A predetermined-length strip was physically folded at the same spot repeatedly until it broke or displayed obvious fissures. The folding endurance value was determined by counting how many times the patch could be folded without breaking. The test verifies that the patch will maintain its structural integrity after multiple applications and packaging operations.

Surface pH

Theskin compatibility of the developed patches is assessed by measuring their surface pH. The patch underwent swelling after it received a small amount of distilled water for a fixed time period. The pH value was measured using a calibrated digital pH meter after the pH electrode had been properly installed on the patch's wet surface. In order toavoid skin irritation and discomfort during extended usage, suitable pH levels are maintained.

Drug Content Uniformity

Thedrug content uniformity testing is conducted to evaluate how evenly miconazole nitrate spread throughout the patch matrix. For this, a specific section of the patch which they dissolved in a suitable solvent system is used to release the transfersomes that were inside the patch. To achieve complete drug extraction from the mixture shaking and sonication methods are used. Spectrophotometric analysis to

examine the solution which they obtained through filtering at the specific λmax measurement point. The standard calibration curve was used to determine the drug content. This assessment validates the formulation method's repeatability and dose accuracy.

In-Vitro Drug Release Study

A diffusion cell equipment fitted with a dialysis membrane or an appropriate synthetic membrane was used to conduct the in-vitro drug release investigation. The membrane required soaking in receptor media before its actual use to ensure proper hydration. The drug-loaded side of the prepared patch was positioned against the membrane in the donor compartment. The receptor compartment received phosphate buffer pH 7.4 together with a suitable methanol proportion to establish sink conditions. The system maintained physiological conditions through operation at 37 ± 0.5°C and continuous magnetic stirrer agitation. And aliquots from the receptor compartment is removed at specific times while using fresh medium to replace the removed samples. Thespectrophotometric analysis measures the amount of medication released from the extracted samples.This method evaluates the release kinetics and sustained delivery behavior of the transdermal patch.

Ex-Vivo Skin Permeation Study

Theanimal skin which had been taken off the animal body is used and put into a Franz diffusion cell to conduct their ex-vivo permeation studies. The patch was placed in the donor compartment while the epidermal side of the skin faced the compartment. The receptor media maintained a continuous swirl motion while being kept at human body temperature. The drug content testing on collected samples at specific times throughout the experiment. This studiesshows how transfersome-loaded patches enhance their ability to penetrate biological membranes and overcome the stratum corneum barrier.

Moisture Content and Moisture Uptake

The moisture content was determined through weighing the patches which were then placed inside a desiccator that contained only anhydrous calcium chloride until they reached constant weight. The percentage moisture content was determined through weight difference measurements. The patches underwent moisture uptake testing under controlled humidity conditions which required their weight to be measured after specific time intervals.

The studies predict storage behavior while they evaluate patch stability under different environmental conditions.

Tensile Strength

The mechanical properties of materials were tested using tensile strength testing equipment. The patch strip was attached between two clamps at its exact measured length and tested until it reached breakage. The force required to break the film is measured. The tensile strength and % elongation to evaluate the mechanical properties of the materialis determined. The material needs sufficient tensile strength to maintain its durability during both application and storage.

Stability Studies

According to ICH recommendations, stability investigations were carried out by keeping the produced patches under various humidity and temperature settings. The physical qualities, drug content, mechanical attributes, and in-vitro release characteristics of the samples were assessed on a regular basis. Stability assessment ensures that the formulation retains its structural integrity and therapeutic effectiveness for an

extended period.

RESULTS AND DISCUSSION

The current research developed and tested miconazole nitrate-loaded transfersomes for use in antifungal delivery through transdermal patches. The following section presents complete results from various physicochemical tests and performance evaluations.

Preformulation Studies

Determination of λmax

The UV spectrophotometric study of miconazole nitrate in phosphate buffer pH 7.4 showed that it reached its highest absorption point at 272.5 nanometers. Thespecific wavelength is selected to conduct three experiments which included in-vitro drug release studies and entrapment efficiency tests and quantitative drug content measurements. The distinct peak confirmed both the drug's purity and the solvent system's suitability for analytical purposes.

Calibration Curve

The standard calibration curve created with phosphate buffer pH 7.4 showed linearity from 2 to 16µg/ml concentration range. The linear regression analysis produced a high correlation coefficient which proved that Beer-Lambert's law was being applied. The method establishes its reliability for use in subsequent analytical measurement processes.

Table 4Standard curve of Miconazole nitrate

Concentration(µg/ml)	Absorbance at 272 nm
2	0.054
4	0.104
6	0.155
8	0.205
10	0.255
12	0.305
14	0.356
16	0.403

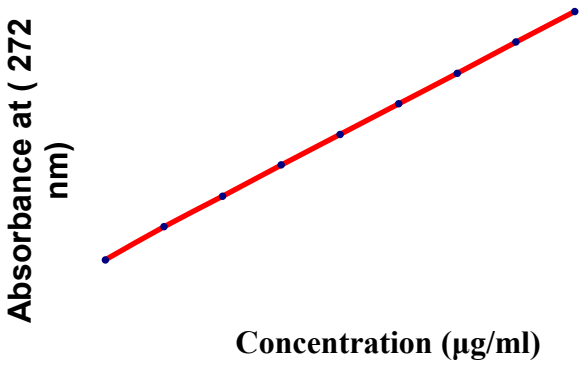

Figure 1: Standard curve ofMiconazole nitrate

Drug–Excipient Compatibility Studies

The FT-IR spectra of pure miconazole nitrate showed unique peaks which corresponded to its functional chemical groups. The drug showed all its unique peaks when it physically combined with phospholipids and cholesterol and edge activators because the peaks remained intact without any shifts or losses. The study demonstrates that the drug remains stable in both the vesicular system and patch matrix because there was no chemical reaction between the drug and excipients during the formulation process.

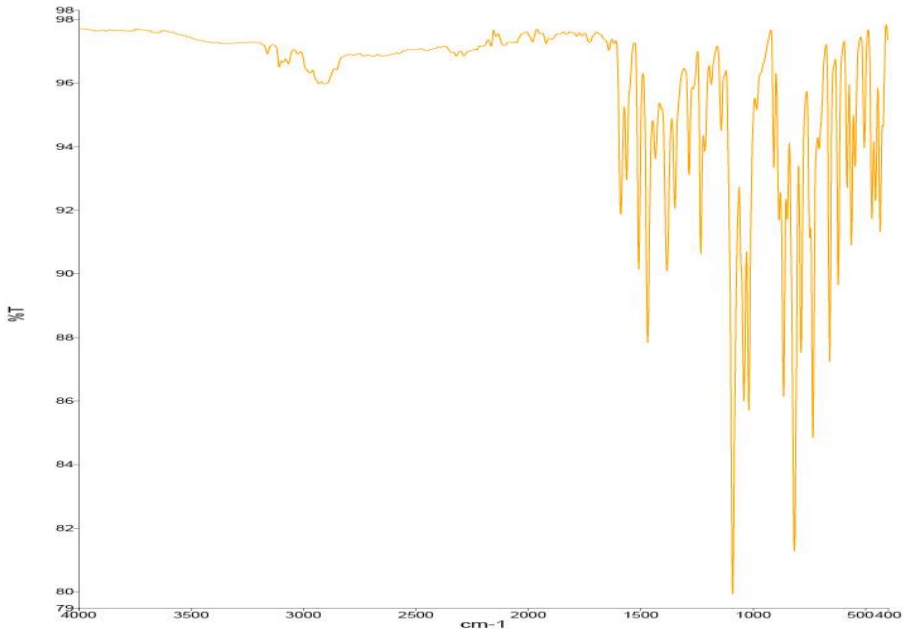

Figure 2: FT-IR spectrum of Miconazole Nitrate

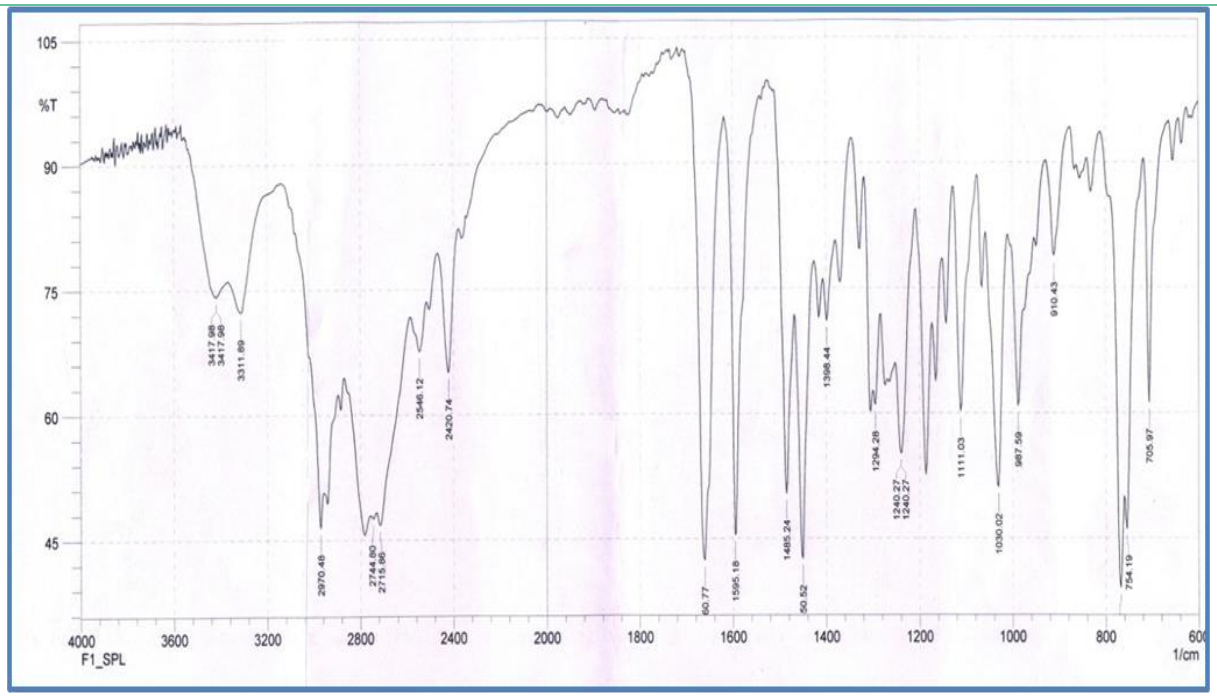

Figure 3 FT-IR spectrum of Propylene glycol

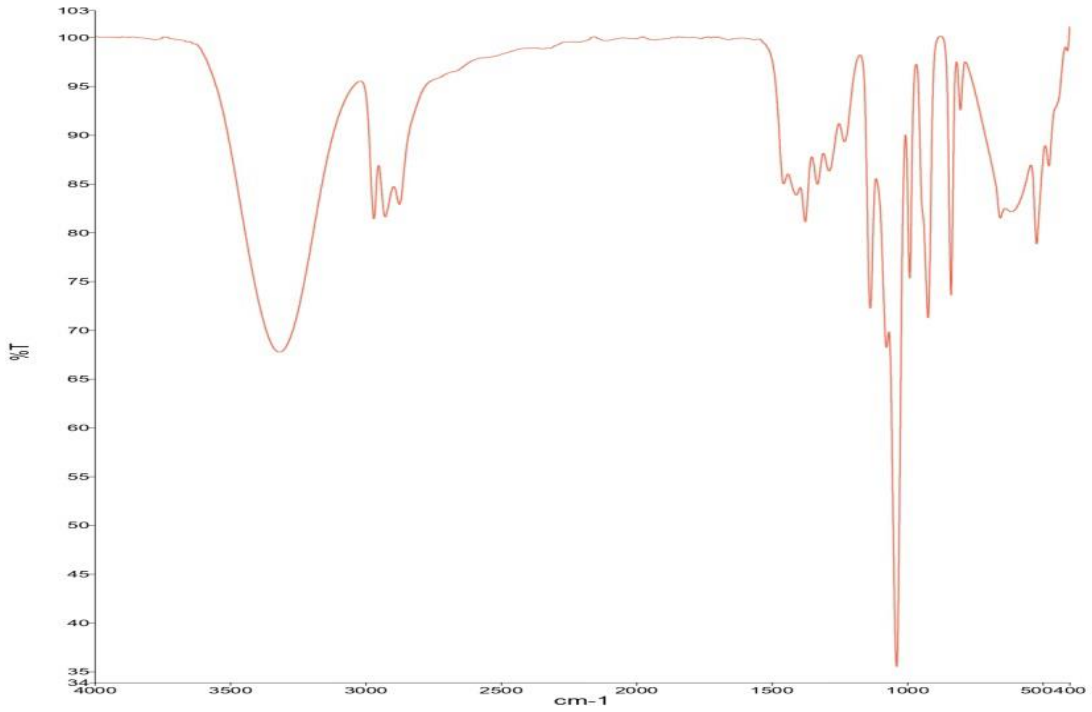

Figure 4: FT-IR spectrum of Soya Lecithin

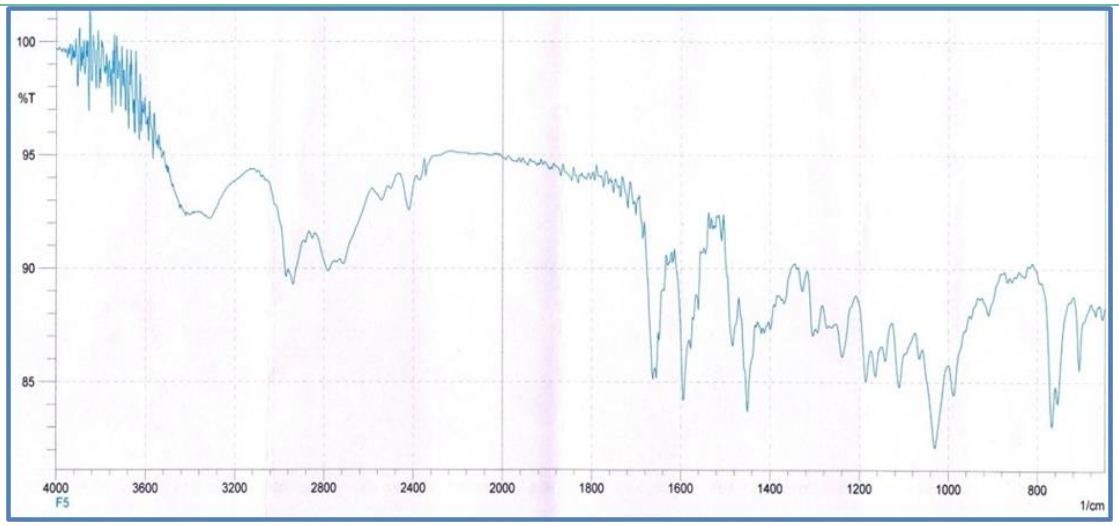

Figure 5: FT-IR spectrum of Physical Mixture

Evaluation of Miconazole Nitrate–Loaded Transfersomes

Morphological Characterization

The analysis at the microscopic level confirmed that the formation of spherical vesicles by the SEM.

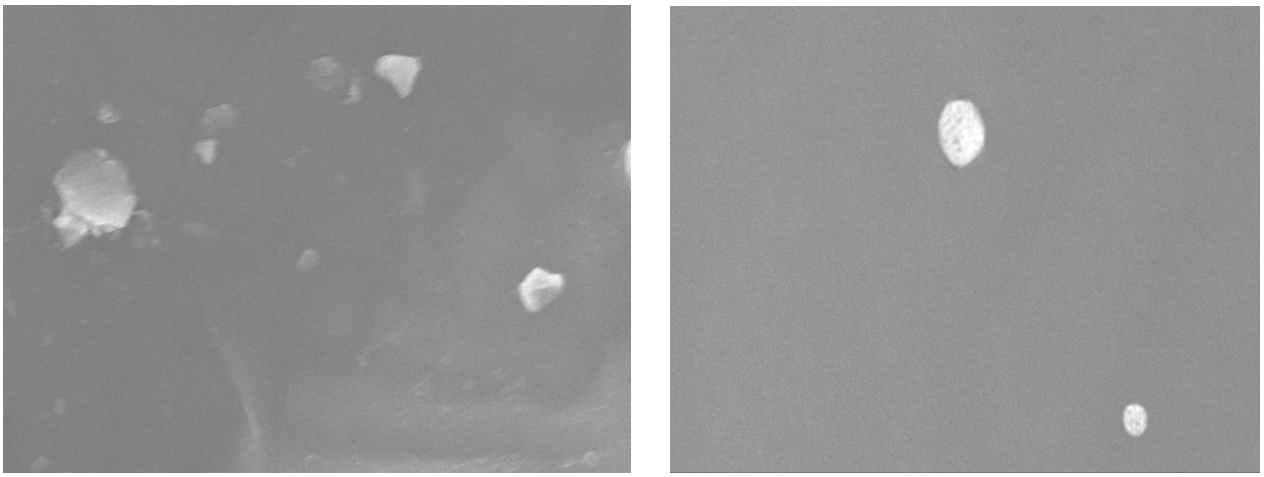

Figure 6: SEM of Optimized Formulation

The vesicles appeared as separate entities which were distributed across the space, demonstrating that the thin film hydration method had successfully produced transfersomes. The vesicular dispersion remains stable because there is no aggregation present.The prepared transferosomes were observed as the perfect spears by SEM.

Particle Size Analysis

All formulations showed measurement results that fell within the submicron range. The average vesicle dimension of the enhanced formulation F-4 measured 187.38 ± 2.61 μm. The decreased vesicle dimensions enable better material flow through the skin and facilitate intercellular lipid pathways to access the stratum corneum. The smaller size of the material creates additional surface area, which enables better drug release and better penetration efficiency.

Table 5: Particle Size distribution of miconazole nitrate Transferosomes

Transfersomes Formulations Code	Average particle Size of Transfersomes (nm)
F1	419
F2	450
F3	430
F4	460

Zeta Potential

The improved formulation F-4 showed a zeta potential measurement of -44.68 ± 1.45 mV. The high negative value demonstrates that vesicles experience strong electrostatic repulsion which prevents their aggregation and maintains their colloidal stability for extended periods. The stability of vesicles plays a critical role in maintaining drug encapsulation until the transdermal patches are applied.

Entrapment Efficiency

F-4 demonstrated the highest entrapment effectiveness of 50.6±1.0%among all formulations. The phospholipid and Span 80 ratio were tuned, which improved the lipid bilayer's flexibility and drug accommodation. The preferred method of attaining high entrapment efficiency delivers continuous medication availability while minimizing drug waste.

Table 6: Entrapment Efficacy of miconazole nitrate Transferosomes

Transfersomes Formulations Code	Percentage of Drug Entrapment
F1	40.0±1.0%
F2	48.7±1.2%
F3	42.6±1.8%
F4	50.6±1.0%

In-Vitro Drug Release of Transfersomes

The improved transfersomal formulation (F-4) reached a cumulative drug release of 99.16 ± 1.62% at the 10-hour mark. The vesicular drug delivery system released its contents through two distinct phases which started with moderate release and continued with steady output. Controlled release happens because drugs get trapped inside the lipid bilayer which then slowly releases them into the surrounding environment. Transdermal delivery systems benefit from extended release because higher encapsulation results in slower drug release according to the relationship between entrapment efficiency and release rate.

Evaluation of Transfersome-Loaded Transdermal Patches

Thephysicochemical properties and operational performance of polymeric transdermal patches that contained the optimized transfersomal formulation F-4 are evaluated.

Physical Appearance

The prepared patches all displayed the same visual characteristics because they maintained flexible properties and their surfaces remained smooth. The objects displayed no surface defects because there were

neither cracks nor air bubbles present. The texture of the material shows that transfersomes distribute evenly throughout the polymer matrix which results in proper film development.

Thickness and Weight Uniformity

The produced patches showed stable weight changes and maintained consistent thickness throughout all tests. The solvent casting method demonstrates its ability to produce consistent results because there was only minimal variation from the expected results which showed that polymeric materials were evenly distributed throughout the process.

Table 7 Physio-Chemical Properties of Transdermal Patches

S. No	Parameters	Results		
		F1	F2	F3
1	Thickness (mm)	0.91±0.04	0.95±0.063	0.95±0.052
2	Weight variation (mg)	37.58±1.07	39.87±1.37	39.98±1.47
3	Percentage of Moisture content (%)	10.45±0.51	11.25±0.61	12.64±0.71
4	Drug content (%)	93	92	95

Folding Endurance

The patches demonstrated excellent mechanical strength through their ability to endure multiple folds without breaking. The patch maintains its structural integrity because of its high folding endurance which protects it from damage during handling and application.

Surface pH

The surface pH of the developed patches showed results which matched the normal skin pH range. The patch maintains skin compatibility through its design which prevents any skin irritation during application.

Drug Content Uniformity

The drug content analysis showed that Miconazole nitrate existed in an even distribution throughout the patch matrix. The drug content analysis showed results between 96 and 99% which indicates that the method produces consistent results with minimal drug loss during the manufacturing process.

In-Vitro Drug Release Study of Transdermal Patch

The in vitro release test demonstrated that transdermal patches containing transfersomes released their drugs at a steady rate for 24 hours. The optimized patch showed superior drug release results when compared to the basic drug patch. The transfersomes' ultra-deformable properties enable drugs to be released through two stages: first diffusional movement through the polymer matrix and then through membrane passage. The polymeric patch and vesicular system work together to control drug release in two ways: first from vesicles and subsequently through polymer diffusion.

Table 8: In-vitro diffusion study of Transdermal Patches (F1 & F2)

S.No	Time (mts)	F1% Drug release	F2 % Drug release	F3% Drug release
1	0	0	0	0

2	30	7.71±1.5	4.89±1.30	4.89±1.30
3	60	10.28±1.56	8.42±1.41	8.42±1.41
4	90	14.78±1.32	12.85±1.75	12.85±1.75
5	120	18.01±1.43	15.71±1.82	15.71±1.82
6	150	22.50±1.21	18.64±1.87	18.64±1.87
7	180	27.07±1.34	24.42±1.91	24.42±1.91
8	210	31.53±1.41	24.42±1.95	24.42±1.95
9	240	35.35±1.56	28.28±1.83	28.28±1.83
10	270	39.85±1.52	32.27±1.87	32.27±1.87
11	300	43.0±1.31	37.28±1.72	37.28±1.72
12	330	47.51±1.32	40.53±1.86	40.53±1.86
13	360	51.42±1.46	45.02±1.89	45.02±1.89
14	390	55.92±1.71	49.51±1.84	49.51±1.84
15	420	60.20±1.79	54.64±1.93	54.64±1.93
16	450	63.06±1.82	57.85±1.98	57.85±1.98
17	480	67.78±1.91	61.71±1.91	61.71±1.91
18	510	72.64±1.97	66.85±1.55	66.85±1.55
19	540	76.50±1.99	70.71±1.42	70.71±1.42
20	570	81.03±1.53	75.21±1.57	75.21±1.57
21	600	86.78±1.56	79.09±1.33	79.09±1.33

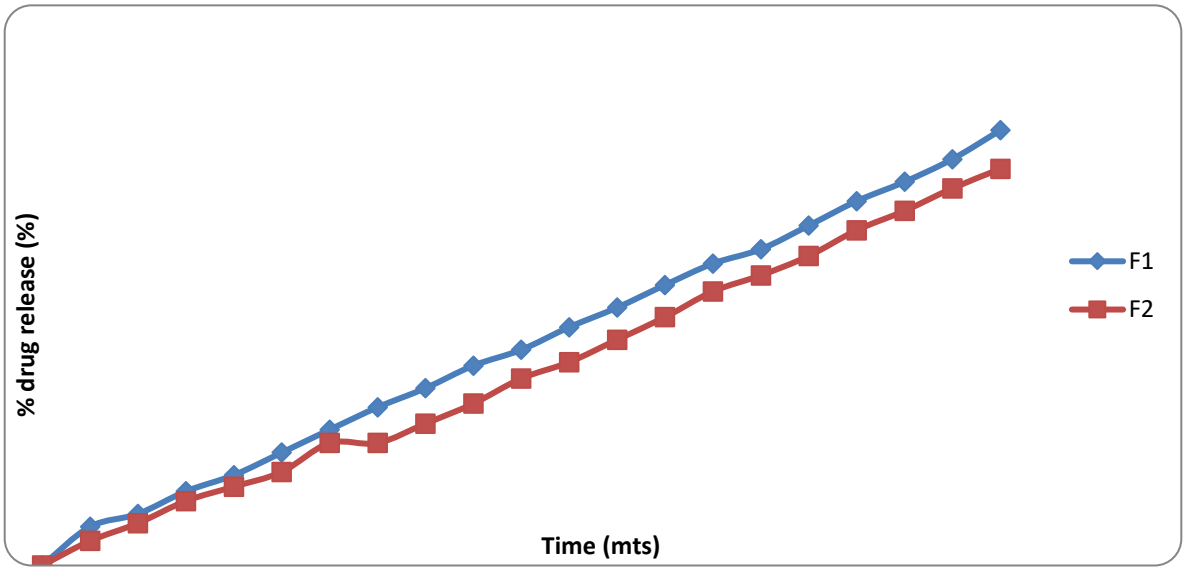

Figure 9In-vitro diffusion studyof Transdermal Patches (F1 & F2)

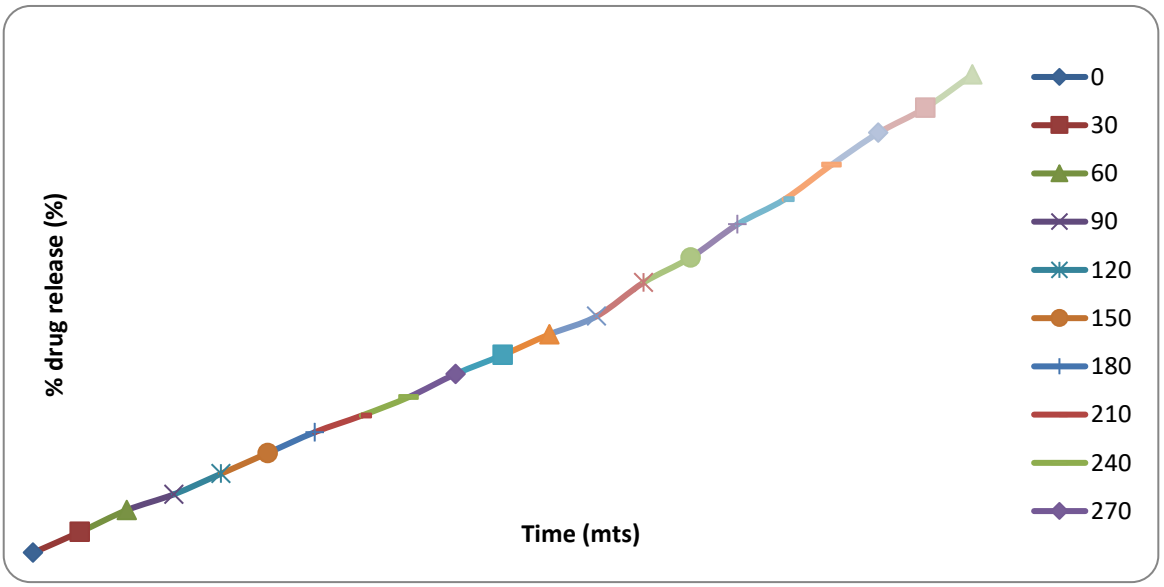

Figure 10 In-vitro diffusion study of Transdermal Patches (F3)

Kinetic Modeling

The multiple kinetic models is applied to analyze the release data which included zero-order and first-order and Higuchi and Korsmeyer–Peppas models. The Korsmeyer–Peppas model had the highest regression coefficient (R2 = 0.9915). The drug release pattern showed non-Fickian diffusion which indicates that two distinct mechanisms operate through diffusion and polymer relaxation processes. The results demonstrate that drugs exit the patch through two mechanisms which involve controlled diffusion from vesicles and gradual erosion or expansion of the polymer matrix.

Stability Studies

The three-month stability tests conducted at 4°C, 25°C, and 37°C demonstrated that the 4°C stored formulations maintained their original entrapment effectiveness and drug content and physical appearance. The elevated temperature is observed and conditions resulted in slight drug content reduction,because vesicles became unstable and released their drug contents. The addition of transfersomes to a transdermal patch resulted in better stability than using dispersion by itself. The polymeric matrix system enhanced formulation stability by restricting vesicle movement and reducing particle clustering effects.

CONCLUSION

The research demonstrates that miconazole nitrate addition to transfersomes leads to better drug release control and higher drug retention. The optimized transfersomes enable their use in transdermal patches, which will enhance product stability, extend delivery duration, and increase antifungal effectiveness.

The developed transfersome-loaded transdermal patch technology successfully bypasses the stratum corneum's natural barrier, offering an effective alternative to standard topical medications. The dual controlled release system provides extended drug effects while requiring fewer doses, which results in improved patient adherence.

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