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FORMULATION, DEVELOPMENT AND EVALUATION OF TRANSFERSOMAL GEL OF MICONAZOLE NITRATE

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Abstract:

Miconazole nitrate (MCN) is an antifungal drug used for treatment of superficial fungal infections. However, it has low skin permeability. Hence, the objective of this study was to prepare miconazole nitrate using transfersomes to overcome the barrier function of the skin. MCN transfersomes were prepared using a thin lipid film hydration technique. The prepared transfersomes were evaluated with respect to morphological study, particle size analysis, zeta potential, % entrapment efficiency and quantity of in vitro drug released to obtain an optimized formulation. The optimized formulation of MCN transfersomes was incorporated into a Poloxamer 407, HPMC K15, propylene glycol gel base which was evaluated for pH, rheological study, content uniformity, in vitro drug release study and stability studies. The average vesicle size of optimized formulation (F-4) observed as 187.38±2.61µm, zeta potential observed as -44.68±1.45mV and %EE was found as 82.86±5.27%. The in vitro release study suggested that there was an inverse relationship between EE% and in vitro release. The kinetic analysis of all release profiles was found to follow Korsemeyer-peppas model. Stability studies for prepared formulations were also performed. Transferosomal vesicles stored at refrigeration condition were physically stable. Therefore, miconazole nitrate in the form of transfersomes has the ability to penetrate the skin, overcoming the stratum corneum barrier.

Keywords: *Transfersomes; Miconazole nitrate; Entrapment efficiency; Poloxamer 407.*

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INTRODUCTION:

Fungi are parasitic microorganisms which can affect the skin and mucous membrane along with generation of systemic infections of various internal organs [1]. Fungal infections of skin or mucous membrane, in majority, promote visits of victims to dermatologists [2]. It has been reported that 20%-25% of human population show presence of skin fungal infections [3]. Incidences of occurrence of skin fungal infection are very high in immunocompromised patients [4]. Skin fungal infections are categorized into superficial, cutaneous, and subcutaneous depending upon the level of tissue invasion [5]. When attack of invading fungi is limited to outermost skin layers only then generated infection is called superficial fungal infection. Tinea versicolor, white piedra, and tinea nigra are examples of superficial fungal infections. Superficial fungal infection leads to increase in the skin pH along with mild scaling, redness, and inflammation at the invading site. The barrier nature of skin becomes poor in such a state [6]. Invasion of parasitic fungus into deeper epidermal skin layer develop cutaneous fungal infection. This infection is also known as dermatomycoses and it may have involvement of skin appendages like nails and hairs [7]. Dermatomycoses can also instigate cellular immune response developing pathological variations in patients [8]. Topical treatment of fungal infections is usually preferred as opposed to systemic treatment, as the drug is delivered directly to the infected site, with decreased side effects and improved patient compliance [9]. However the stratum corneum, which is the outermost layer of the skin, represents the main barrier for drug penetration. Hence it is necessary to design a drug delivery system for antifungal drugs which has the ability to overcome the barrier properties of the stratum corneum [9, 10]. Miconazole nitrate is one of the broad spectrum antifungal compounds of the imidazole group [11]. This antifungal agent is a fungicide used in the treatment of fungal infections in a topical and transdermal [12]. This drug works by inhibiting ergosterol biosynthesis on the fungal cell membranes that cause damage to the cell wall of the fungus, resulting in increased membrane permeability, and ultimately, causing the fungal cell to lose its cellular nutrients. The drug is mainly used for the treatment of mycosis skin diseases [13]. The bioavailability of miconazole nitrate is very low when taken orally because it is very difficult to dissolve and has a small absorption, and therefore, the use of miconazole nitrate as an antifungal agent is given topically, but the main problem of this drug in topical treatment is poor skin penetration [14]. Conventional formulations are given in higher doses to overcome this issue and compensate for low permeability. In recent years, the use of lipid vesicles as carriers for topical drugs has attracted great attention due to their ability to overcome the barrier properties of the skin [15]. Transfersomes are ultra-flexible vesicles with a bilayer structure. They can penetrate the skin easily and overcome the barrier function by squeezing through the intracellular lipid of the stratum corneum [16]. After application of transfersomes on the skin, they move from the dry stratum corneum to a deep hydrated layer according to the osmotic gradient. The presence of surfactant in their structure helps in solubilizing the lipid in stratum corneum and permits high penetration of the vesicles [15]. The aim of this study was to prepare and evaluate miconazole nitrate transfersomal gel to enhance skin penetration and increase antifungal activity.

Experimental Section:

Materials:

Miconazole nitrate was a gift from GlaxoSmithKline Pharmaceuticals Limited, Mumbai. Cholesterol, soybean lecithin , sodium cholate was purchased from S. D. Fine Chem. Ltd., India. Span 80, Brij-35, hydrochloric acid was obtained from the Loba Chemie Pvt Ltd, Mumbai, India. Chloroform, methanol, disodium hydrogen ortho phosphate was obtained from Rankem, Pharmaceutical Company Gurgaon, Haryana. Dialysis membrane of Mol Wt cutoff 1200 was purchased from Himedia Laboratory, Mumbai. Dematerialized and double distilled water was prepared freshly and used whenever required. All other reagents and chemicals used were of analytical grade.

Preformulation study:

Determination of λmax:

A solution of MCN containing the concentration 10µg/ml was prepared in PBS pH 7.4 and UV spectrum was taken using double beam spectrophotometer (Systronic, 2200). The solution was scanned in the range of 200-400 nm.

Preparation of standard calibration curve of MCN in PBS 7.4 pH buffer:

Accurately weighed 10 mg of drug was dissolved in 10 ml of 7.4 pH buffer solution in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 7.4 pH buffer solution. Prepare suitable dilution to make it to a concentration range of 5-25µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Systronic, 2200). A graph of concentration Vs absorbance was plotted.

Drug-excipients interaction studies by FTIR:
Infra-red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tones pressure. It was scanned from 4000 to 150 cm^{-1} in a Bruker FTIR spectrophotometer. The FTIR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

Preparation of MCN -loaded transfersomes:
Transfersomes formulations were prepared by a thin film hydration method [17, 18]. Soybean phosphatidylcholine, cholesterol, sodium cholate, span 80, and brij 35 with different molar ratios were dissolved in 10 ml of a mixture of three organic solvents (methanol: chloroform: ethanol) at (2:2:1) v/v/v ratio, as represented in Table 1. Using rotary evaporator, thin lipid film on the internal surface of the round-bottomed flask was formed. MCN (100 mg) was dissolved in 20 ml of an isotonic phosphate buffer (pH 5.8). MCN solution was used to hydrate the prepared thin film by rotation at 100 rpm for 2 hours. To form large multilamellar vesicles, the resulting suspensions were kept for 24 hours at 25°C. To form smaller vesicles, the transferosomal dispersions were sonicated for 30 minutes. The MCN transfersomes were separated from the entrapped MCN by high-speed centrifugation at 20,000 rpm for 3 hours at −5°C using cooling ultracentrifuge. To separate the untrapped MCN, clear supernatant was carefully taken out after the centrifugation. The transfersomes remained as precipitate containing the entrapped MCN. The precipitate was resuspended in 10 ml of isotonic phosphate buffer (pH 5.8) in order to be evaluated. The transferosomal dispersions (free from the untrapped MCN) were kept at a constant temperature of 4°C within glass vials. Laminar air flow hood was used for conducting experimental procedures under aseptic conditions.

Table 1 Composition of transfersomal formulations

F. code	MCN	Cholesterol	Lecithin	Sodium cholate	Span 80	Brij 35
F-1	100	2	1	4	-	-
F-2	100	2	1	3	-	-
F-3	100	2	1	2	-	-
F-4	100	2	1	-	4	-
F-5	100	2	1	-	3	-
F-6	100	2	1	-	2	-
F-7	100	2	1	-	-	4
F-8	100	2	1	-	-	3
F-9	100	2	1	-	-	2

Formulation of transferosome entrapped MCN gel
The gel was prepared by the same procedures described by Schmolka (1972) [20]. In brief, in 10 ml distilled water, required quantities of poloxamer 407 and HPMC K15 were added slowly and stirred with the help of magnetic stirrer at 50 rpm for 1 hour. To ensure the maximum dissolution of polymers, the prepared solution was left in the quiescent state for 12 hours in a refrigerator. Then, the solution (poloxamer with HPMC K15) was stirred slowly at 5°C for 5 hours until a gel was formed. Various formulations were prepared as shown in Table 2.

Table 2 Composition of transfersomal gel formulations

Formulation code	Poloxamer 407	HPMC k15	Propylene glycol	DMSO
FG-1	10	15	-	-
FG-2	10	20	-	-
FG-3	10	25	-	-
FG-4	10	20	0.5	-
FG-5	10	20	-	0.5

Evaluation of transfersomal formulations [19]:

Morphological study:

The vesicle formation was confirmed by optical microscopy in 45× resolution. The Transfersomal suspension placed over a glass slide and fixed over by drying at room temperature, the dry thin film of Transfersomal suspension observed in the formation of vesicles. The microphotography of the transferosomes also obtained from the microscope by using a digital camera. The detailed surface characteristic of the selected transferosome formulation was observed using a scanning electron microscope.

Particle size analysis:

The vesicle sizes of transferosome were determined by light scattering based on laser diffraction using a Malvern Master sizer (Malvern Instruments, Malvern, UK). The apparatus consisted of a HeNe laser (5 mW) and a small-volume sample-holding cell. The sample was stirred using a magnetic stirrer bead to keep and maintain the sample in suspension.

Zeta potential:

The significance of zeta potential is that its value can be related to the stability of colloidal dispersions. The zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion. The zeta potential for the transfersomal dispersion was determined using Malvern instruments.

Entrapment efficiency:

The percentage of MCN loading in transfersome was determined by using 4.0 ml of dispersion. Free MCN was separated from the transferosomal dispersions by subjecting the transfersomes to a high-speed centrifugation at 21,000 rpm at 10°C model T-70BL (Laby Instrument Industry, Haryana, India) for 3 hours. The supernatant was siphoned-off and analyzed using a UV spectrophotometer. The precipitate separated from supernatant was re-dispersed in 4 ml of phosphate buffer (pH 7.4). To perform the lysis of transfersomes for liberating the encapsulated MCN molecules, a 500 µL was diluted ten times with methanol. The concentration of drug was determined spectrophotometrically.

$$\% \text{ Entrapment efficiency} = [(TD-FD)/TD] \times 100$$

Where TD is the total drug amount, and FD is the amount of free drug.

***In-vitro* drug release study:**

The *in vitro* release study was performed via a dialysis membrane. Briefly, an equivalent amount of 10 mg MCN -loaded transferosomal dispersion was introduced into dialysis bags with a molecular weight cutoff 12,000 kDa. The dialysis bags were suspended in an buffer solution (250 ml, pH 7.4, 37°C±2°C) at speed of rotation 1,500 rpm and placed within the dissolution flask of the USP dissolution apparatus. The samples (5 ml) were withdrawn and analyzed spectrophotometrically every 45 minutes for 12 hours. The withdrawn samples were replaced with the same volume of fresh a buffer solution (pH 7.4). The concentration percentage of MCN at time (t) was estimated.

Evaluation of transfersomal gel [21]:

Physical appearance:

The prepared gel was examined for clarity, color, homogeneity and the presence of foreign particles.

Ph:

The pH of the dispersion was measured by using a digital pH meter.

Rheological study:

Viscosity was determined by Brookfield programmable DV III ultra viscometer. In the present study, spindle no. CP 52 with an optimum speed of 0.01 rpm was used to measure the viscosity of the preparation.

Content uniformity:

The drug content of the prepared gel was carried out by dissolving accurately weighed quantity of gel equivalent to 10 mg of the drug and triton X-100 (1%) in small amount of water shaken it vigorously and taken in 100 ml volumetric flask and volume was made up to 100 ml with methanol. The content was filtered through Whatman filter paper No. 41. 5 ml of above solution was taken into a 25 ml volumetric flask and volume was made up to mark with methanol. The content of MCN was determined against blank by using the Systronic, 2200 UV/visible spectrophotometer. The drug content was determined from the calibration curve of drug.

***In vitro* drug release study:**

The apparatus consists of a glass cylinder open at both ends. A dialysis membrane soaked in distilled water (24 h before use) is fixed to the one end of the cylinder with the aid of an adhesive. Gels equivalent to 10 mg of drug is taken inside the cell (donor compartment) and the cell is immersed in a beaker containing 100 ml of PBS pH 7.4 containing 10% v/v methanol (to maintain sink condition), act as receptor

compartment. The whole assembly is fixed in such a way that the lower end of the cell containing gel is just above the surface of the diffusion medium (1-2 mm deep) and the medium was agitated using a magnetic stirrer at the temperature 37 ± 0.5°C. Aliquots (5 ml) are withdrawn from the receptor compartment periodically and replaced with same volume with fresh buffer. The samples were analyzed by using UV-visible spectrophotometer. The tests were carried out in triplicate.

Kinetic modeling of *in -vitro* release rates of formulations:

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

Zero-order kinetic model-cumulative percentage drug release versus time.

First- order kinetic model-log cumulative percentage drug release remaining versus time.

Higuchi's model-cumulative percentage drug released versus square root of time.

Korsmeyer's equation/peppa's model-log cumulative percentage drug released versus log time.

Stability studies:

As soon as the product is developed, it is subjected to ageing; as a result its physical properties, chemical composition and even its biological availability may be changed. To assess long-term stability, formulation was stored in gel tube at 4±1°C, 25±2 °C and 45±2 °C for a period of 3 month. They were evaluated for the following parameters: Appearance, Viscosity pH, drug content analysis, % drug release [22].

RESULTS AND DISCUSSION:

The λ_{max} of MCN was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer (Systronic, 2200) using 7.4 pH buffer solution as solvent was found to be 272.5. The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in Fig. 1. All transferosomal formulations were found to be in the sub-micron to nanosize range. The optimized formula F-4 showed the highest percent encapsulation entrapment (82.86±5.27%), mean particle size 187.38±2.61µm and zeta potential -44.68±1.45mv.The formula F-4 was used to be incorporated to formulate gel, the results shown in Table 3. The release of drug from transfersomal formulations were determined using membrane diffusion technique. The result of *In vitro* drug release study of transfersomal formulation was given in Table 4. Results of evaluation of transfersomal gel formulation (FG-1-FG-5) of optimized formulation (F-4) were incorporated into the prepared gel. PG and DMSO were used as skin permeation enhancers. All formulations had off-white appearance. The pH of the formulated gels of HPMC and different permeation enhancers was found between 5.88 and 7.38. All the examined gel samples exhibited good viscosity & drug content (%) in the range of 10.56 - 24.12and 96.66-98.85 respectively. The comparative permeation of miconazole nitrate from miconazole nitrate-containing plain gel, FG-4 & FG-5 formulations has also been shown, significant increase in the permeation Table 6. Kinetic treatment of the release was also performed. Release kinetics analysis demonstrated a maximum R^2 values corresponding to Korsmeyer-Peppas, which indicate a delayed drug release behavior of gel formulation following diffusion and erosion behavior confirmed by Korsmeyer-Peppas exponent value Table 7. Stability studies for prepared formulations were also performed. The determinations of entrapment efficiency of different transfersomes, which were stored at 4°C, 25°C, and 37°C over a period of 3 months. The findings of stability study suggested that storage of transfersome at 4°C may enhance stability of transfersomes. Embedding transfersome into gel may support stability of transferosomal vesicles as a result of increasing viscosity of the carrier, reducing possibility of infusion.

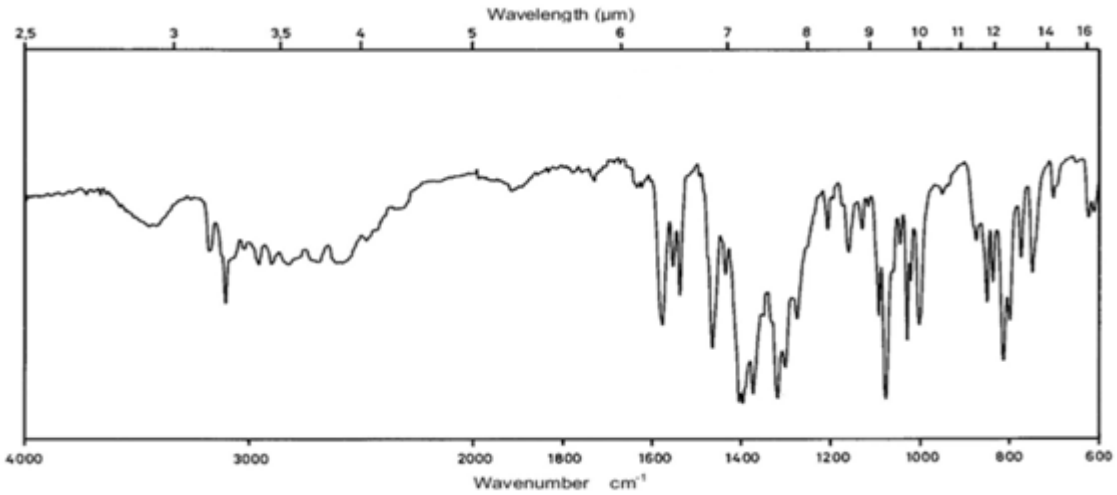

Figure 1 FT- IR spectra of MCN

Table 3 Evaluation of MCN loaded transfersomal formulation (F-5)

Formulation Code	Mean particle size (μm)	Zeta potential (mv)	Encapsulation efficacy (%)
F-4	187.38±2.61	-44.68±1.45	82.86±5.27

Table 4 Cumulative % of drug release of MCN loaded transfersomal formulation

F. Code / Time	Cumulative % of drug release (in 10 hr.)				
	F-4	**F-5**	**F6**	**F-7**	**F-8**
0	0	0	0	0	0
0.25	19.32±2.23	17.35±4.66	22.97±4.35	19.33±2.15	18.91±1.35
0.5	29.67±3.86	15.96±4.53	36.54±3.66	19.89±4.35	15.59±1.39
1	35.09±2.06	25.97±3.79	41±5.39	31.69±3.29	27.67±2.38
2	47.86±3.56	33.53±3.43	48±7.21	37.58±3.09	35.54±2.98
3	62.33±2.98	44.79±3.08	58.25±3.63	46.19±2.56	41.78±2.32
4	67.95±3.54	51.44±1.69	63.86±9.52	54.18±2.33	52.99±2.67
5	79.43±3.08	60.72±3.23	76.51±8.35	65.84±3.67	68.95±1.08
6	88.11±2.15	74.27±2.66	82.35±2.45	73.94±2.65	79.55±2.18
8	96.56±2.86	89.64±2.23	94.45±1.74	80.89±1.09	81.95±2.78
10	99.16±1.62	96.28±4.35	95.83±2.17	89.76±4.86	90.11±1.96

Table 5 Evaluation of MCN loaded transfersomal gel formulation

Formulation Code	FG-1	FG-2	FG-3	FG-4	FG-5
Appearance	Off-white	Off-white	Off-white	Off-white	Off-white
Homogeneity	Good	Good	Good	Good	Good
pH	5.88	6.55	7.38	6.76	5.26
Viscosity (Pascal Second)	10.56	16.95	24.12	20.68	17.85
Drug Content (%)	96.66	98.85	97.28	98.56	98.47

Table 6Cumulative % of drug release of MCN loaded transfersomal gel formulation

Time in(hrs)	Plain Gel	FG-2	FG-4	FG-5
0.25	0	0	0	0
0.5	0	0	0	0
0.75	0	0	0	0
1	0.85±0.12	0.67±1.15	0.93±0.11	2.14±0.55
1.5	1.701±0.68	1.56±0.89	1.861±0.34	4.56±0.67
2	2.552±0.55	2.56±1.34	3.72±0.56	7.85±0.89
2.5	7.658±0.98	5.67±1.7	11.96±0.98	12.87±1.26
3	12.76±1.05	10.11±1.21	16.54±1.15	19.45±1.75
4	18.45±1.23	13.56±1.15	22.85±1.18	25.78±1.89
5	22.97±1.56	22.87±1.24	38.09±1.25	40.45±1.94
6	29.78±1.78	31.46±1.31	43.74±1.14	45.8±1.48
7	30.63±1.34	39.89±1.52	54.6±1.31	55.23±2.13
8	31.88±1.54	45.15±1.48	60.47±1.45	65.78±1.82
9	32.29±1.67	49.55±1.36	70.26±1.98	78.67±1.95
24	36.48±1.53	52.67±1.29	80.77±1.85	84.67±2.35

Table 7 Kinetic Modeling fitting Miconazole Nitrate Loaded Transfersome Gel Formulations (FG-5)

F. Code	Model	Kinetic Parameter Value	
	Zero order	y = 8.4438x - 5.9999	R^2 = 0.9643
FG-5	First order	y = -0.0452x + 2.0353	R^2 = 0.9369
	Higuchi	y = 22.27x - 18.223	R^2 = 0.8744
	Korsemeyer-peppas	y = 0.7618x + 1.0746	R^2 = 0.9915

CONCLUSION:

Transfersomes were prepared and optimized on the base of average vesicle size and % drug entrapment. The optimized formulation was further incorporated with gel base and characterized for their viscosity, pH, % drug content, and drug release study. The average vesicle size of optimized formulation (F-4) observed as 187.38±2.61µm, zeta potential observed as -44.68±1.45mV and %EE was found as 82.86±5.27%. The preparation of MCN as transfersomal gel has the ability to overcome the barrier properties of the skin and increase the antifungal activity.

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