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TRANSFEROSOMES: A NOVEL APPROACH TO DELIVER OF MICONAZOLE NITRATE FOR TOPICAL PREPRATION

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ABSTRACT

Transferosome of Miconazole nitrate were formulated and evaluated to improve the permeability, site specificity and retention time of the miconazole nitrate with specific emphasis on bioavailability enhancement. Transferosome of miconazole nitrate were prepared by using a various variable parameters like Phospholipids (Soya phosphatidylcholine) in the ratio of 400:450:500:600:650 , surfactants 3.5:1:1.5:2:2.5 and Organic solvents in the ratio of 1:2. Transferosome of miconazole nitrate for different formulations (T1, T2, T3, T4 and T5) were evaluated by particle size, particle morphology, pH, zeta potential, drug content, drug entrapment, and *in-vitro* drug release. The formulation of T2 was found to be optimized from all the formulations prepared.

KEYWORD: Transferosome, Topical route, Phospholipid, Surfactant, stratum corneum, *in-vitro.*

INTRODUCTION

Topical drug delivery system[1,8]

Topical drug delivery system is a form of localized drug delivery system which applied to the surface of skin for its local and systemic effects, but most of these drug delivery systems have been reported to cause skin irritation due to contact dermatitis by the drug and excipients, poor permeability of some drugs through the skin, possibility of allergenic reactions, used only for those drugs which require very small plasma concentration, Enzymatic degradation, Larger particle size of the drugs are not easy to absorb through the skin.

TRANSFEROSOMES[2-7]

Transferosomal is a novel vesicular drug carrier system, which is composed of phospholipids, surfactant, organic solvent and buffering agent. Each transfersome made up of at least one inner aqueous compartment, which is surrounded by the lipid bilayer with specially tailored properties, due to the fusion of "edge activators" into the vesicular membrane. The surfactant such as Tween 20 are commenly used edge activators**.** Transferosomes penetrate the stratum corneum by either the intracellular route or the transcellular route with the excellent distribution properties, transferosomes are widely used as a carrier for the various proteins, anti fungal drugs, anti cancer drugs, analgesics, anesthetics, corticosteroids, sex hormone, insulin, albumins etc.

None the less transferosomes are reported to be non- toxic, biocompatible and biodegradable, target organs for delivering drugs, protect the encapsulated drug from the metabolic degradation, hydrophilic and lipophilic drugs can be encapsulated, high deformability that gives the better penetration of intact vesicles, self adaptable, parenteral and topical drug delivery system, systemic as well as topical drug delivery of drug and easy to scale up.

Therefore current study was under taken to prepare and evaluate transferosome of Miconazole nitrate to eliminate problems associated with traditioal topical drug delivery system and further to improve the bioavailability of Miconazole nitrate with minimum possible side effects.

MATERIAL AND METHOD

Miconazole nitrate was procured from Yarrow Chem Products Mumbai, Dialysis membrane 70 was purchased from Himedia Laboratories PVT. LTD. Soya phosphatidyl choline was purchased from Ottochemika, Mumbai, Methanol and Choloroform were purchased from Finar limited, Ahmedabad (Gujarat). All other chemicals used were of analytical grade.

FORMULATION OF TRANSFEROSOME OF MICONAZOLE NITRATE

Tranasferosome of Miconazole nitrate for different formulations (T1, T2, T3, T4 and T5) were prepared by thin film hydration technique. Phospholipid (Soya phosphatidylcholine) in the ratio of (400:450:500:600:650) was accurately weighed and dissolved in the ratio of chloroform **:** methanol (1:2) in round bottom flask. The resulting solution was then rotated in vacuum rotatory evaporator at 60 rpm and evaporated at 35 ± 2^{0}C to get thin film around the round bottom flask. The obtained dried film was hydrated with PBS (pH 7.4) 30ml containing Miconazole nitrate. The dispersion was then sonicated by ultrasonic bath sonicator for 30 min

to form the transferosomes. The compositions of transferosomes of Miconazole nitrate for different formulations are shown in table no: 1.

Table 1: Composition of Transferosomes of Miconazole nitrate

S.No.	Ingredients	Formulation Code				
		T1	T2	T3	T4	T5
1.	Miconazole nitrate (mg)	100	100	100	100	100
2.	Soya phosphatidylcholine (mg)	400	450	500	600	650
3	Surfactant (Span 20)%	3.5	1	1.5	2	2.5
4	Cholesterol (mg)	55	40	45	30	35
5	Chloroform: Methanol (30 ml)	1:2	1:2	1:2	1:2	1:2
6	Phosphate buffer pH 7.4 (ml)	30	30	30	30	30

Evaluation of Transferosomes of Miconazole nitrate

Clarity: Clarity was determined under fluorescent light against a white and black back ground for presence of any particulate matter.

pH: The pH of the prepared formulations after addition of all the ingredients was measured by using pH meter.

Drug Content Analysis

Transferosomal suspension (1 ml) was taken and dissolved in 100ml phosphate buffer pH (5.5) and shaken vigoursly for 2 hr in magnetic stirrer, there after the resultant solution was filtered and 1ml of sample was withdrawn and diluted to 10 ml in a volumetric flask and the absorbance was recorded in UV spectrophotometer at 272 nm.

Drug Entrapment Efficiency

The entrapment efficiency (EE), which corresponds to the percentage of Miconazole nitrate encapsulated within and adsorbed on to the Transferosomes, was determined by measuring the concentration of free Miconazole nitrate in the dispersion medium. 1.0 ml of the Transferosome was diluted up to 10 ml with phosphate buffer (pH 5.5) and centrifuged at 14000 rpm for 1 hour to separate the lipid and aqueous phase. Supernatant was than filtered by 0.2µ membrane filter and analyzed by UV-VIS spectroscopy at 272 nm.

$$\% EE = \frac{[\text{Initial drug} - \text{Free drug}]}{\text{Initial drug}} \times 100$$

Where,

Initial drug = mass of initial drug used for the assay.

Free drug = mass of free drug detected in the supernatant after centrifugation of the aqueous dispersion.

Vesicle size and zeta-potential

Vesicle size of the transferosome can be determined by Malvern instrument and the Zeta potential of the formulation can be measured by Malvern zeta sizer.

***In-vitro* release studies**

The *In-vitro* release studies of the formulations were determined by the diffusion cell. The diffusion medium of 250 ml phosphate buffer pH (5.5) was used and was stirred at 50 rpm for 37ºC±0.5ºC. One end of the diffusion tubes were covered by a dialysis membrane. Then 5 ml of transferosomal formulations were filled in test tubes that covered with a dialysis membrane and then placed it just touching the diffusion medium that present in the receptor compartment. The drug samples were withdrawn at the interval of half an hour for the period of 12 hrs from the diffusion medium and then analyzed by UV spectrophotometer at 272 nm using the phosphate buffer pH(5.5) as a blank.

RESULT AND DISCUSSION

FTIR (Fourier Transform Infrared Spectroscopy)

All the major peeks observed in miconazole nitrate + lipid , miconazole nitrate + cholesterol , miconazole nitrate + carbopol 940 and miconazole nitrate + methanol were similar as recorded in miconazole nitrate alone. The IR spectra indicate there are no interactions between drug and excipient. These results are depicted in figure no:1- 4.

pH

The pH of the different formulatins (T1-T5) were recorded in the range of 5.1-6.24, the pH of the formulations T1, T2, T3 and T4 are increasing order and there after a decrease was observed. The pH of the optimized formulation (T2) is 5.41 are shown in table no 4.

Drug content and % entrapment efficiency

The drug content and entrapment efficiency of different formulations (T1-T5) were recorded, the drug content of the optimized formulation T2 is 95.25 and the entrapment efficiency of the optimized formulation T2 is 78.1 are shown in table 5.

In-vitro drug release study

In-vitro drug release study of the drug and formulations (T1-T5) are depicted in the figure 7 and shown in table no. 6 and the figure no. 8, the *In-vitro* drug release study of optimized formulation T2 is 71.22.

Vesicle size and zeta potential

Vesicle size and zeta potential of the transferosomes were determined by dynamic light scattering (DLS) by using Malvern Zeta meter. The vesicle size and zeta potential of the optimized formulation T2 is 152.4 and –28.8 are shown in table no.3.

Table 2: Calibration Curve Data of Miconazole nitrate in methanol

S. No.	Concentration (µg/ml)	Absorbance (Mean±S.D.)
1	10	0.1295±0.0007
2	20	0.198±0.0014
3	30	0.3125±0.0021
4	40	0.406±0.0042
5	50	0.5035±0.0021
6	60	0.616±0.0028
7	70	0.707±0.0028
8	80	0.8245±0.0021
9	90	0.8845±0.0035
10	100	0.962±0.0028

Table 3: Zeta poential and particle size values of optimized formulation

Formulation code	Particle size	PDI	Zeta Potential
T2	152.4	0.189	-28.8

Table-4: Determination of clarity and pH data

Formulation	Visual appearance	pH (at 25°C)			
		1st	2nd	3rd	pH (Mean ±S.D.)
T1	Turbid	5.3	5.31	5.32	5.31±0.01
T2	Turbid	5.4	5.42	5.42	5.41±0.011547
T3	Turbid	5.63	5.65	5.66	5.64±0.015275
T4	Turbid	6.23	6.24	6.23	6.23±0.005774
T5	Turbid	5.14	5.16	5.1	5.133±0.030551

Table 5: Determinatin of drug content and enterapment efficiency data

S.no.	Batch code	% Drug content	% Drug content
1	T1	79.87	65.97
2	T2	95.25	78.1
3	T3	91.87	72.05
4	T4	87	66.48
5	T5	80.25	61.77

Table 6: Percentage Cumulative Release of Transferosome of Miconazole nitrate

Time	% Cumulative Drug Release				
	T1	T2	T3	T4	T5
0.5	1.72	8.391	9.466	0.861	3.227
1	7.35	14.58	11.59	12.07	14.26
2	13.1	18.36	18.3	19.6	20.08
3	16.8	27.47	23.6	28.14	23.85
4	24.9	32.38	31.66	31.97	30.37
5	29.1	36.14	39.78	35.7	32.65
6	33.7	43.09	51.56	42.87	36.14
7	37.5	49.04	59.32	52.05	41.16
8	42	54.54	62.27	57.18	45.13
9	46.2	56.58	64.69	63.3	53.81
10	49.1	61.35	65.6	64.93	60.22
11	57.3	65.96	66.48	66.03	61.64
12	62.4	71.22	67.57	66.91	62.74

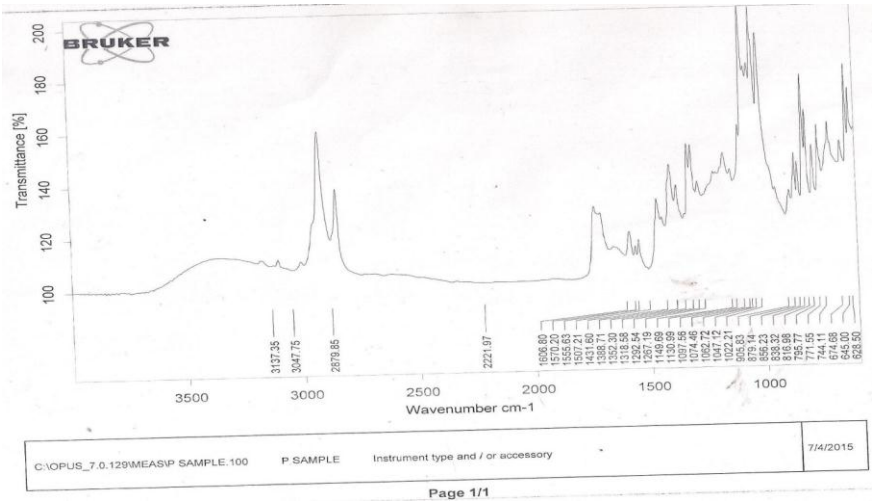

Fig. 1: FTIR Spectra of Miconazole Nitrate

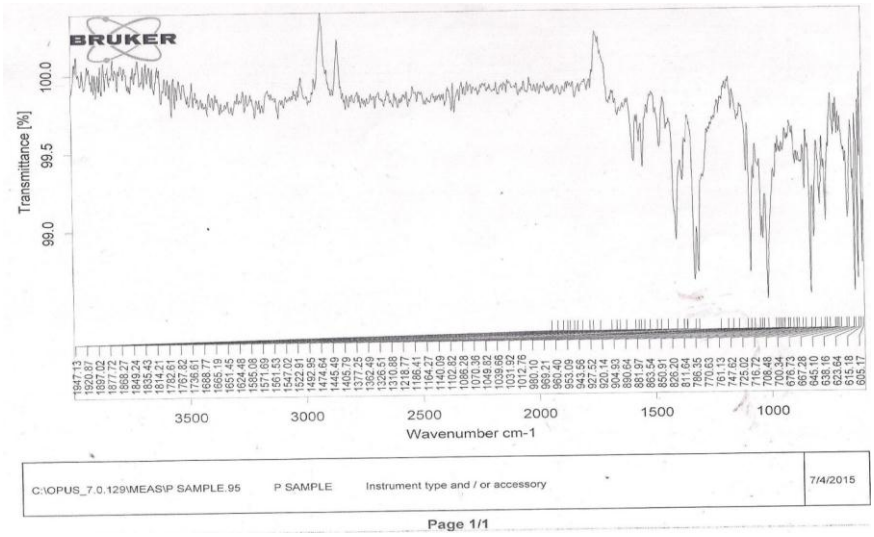

Fig. 2: FTIR Spectra of Miconazole Nitrate + lipid (Soya phosphatidylcholine)

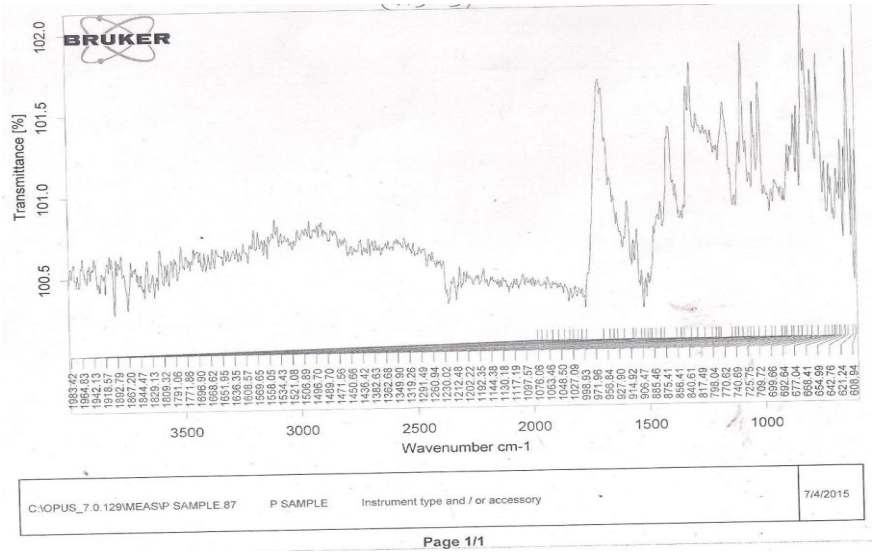

Fig. 3: FTIR Spectra of Miconazole Nitrate + Cholesterol

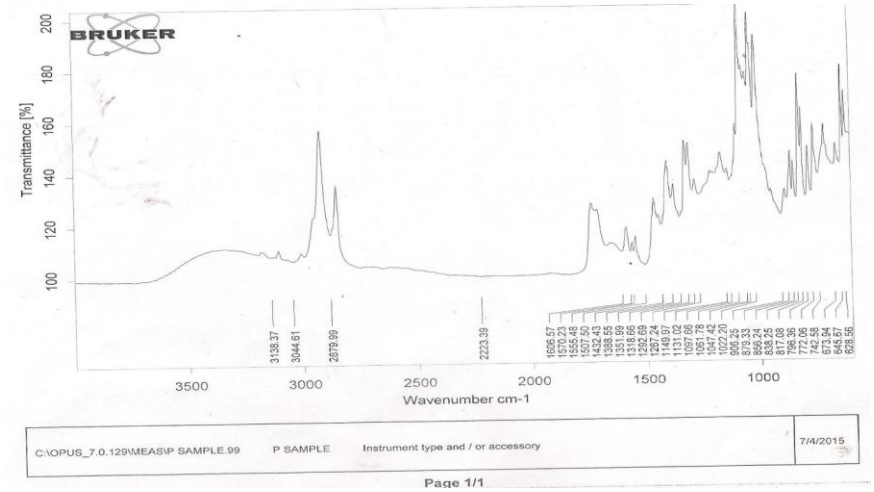

Fig. 4: FTIR Spectra of Miconazole Nitrate + Carbopol 940

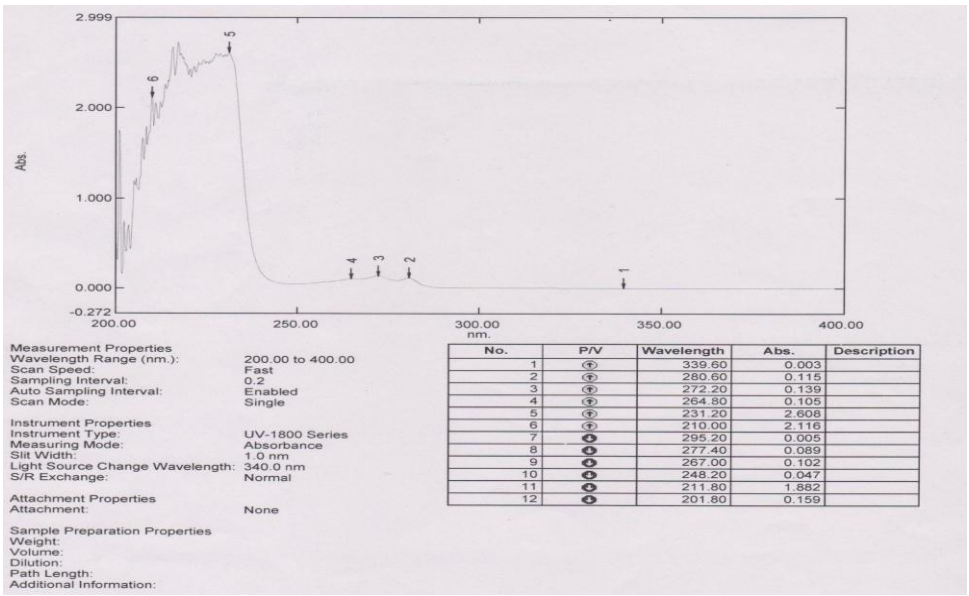

Fig. 5: UV Spectrum of Miconazole nitrate in Methanol

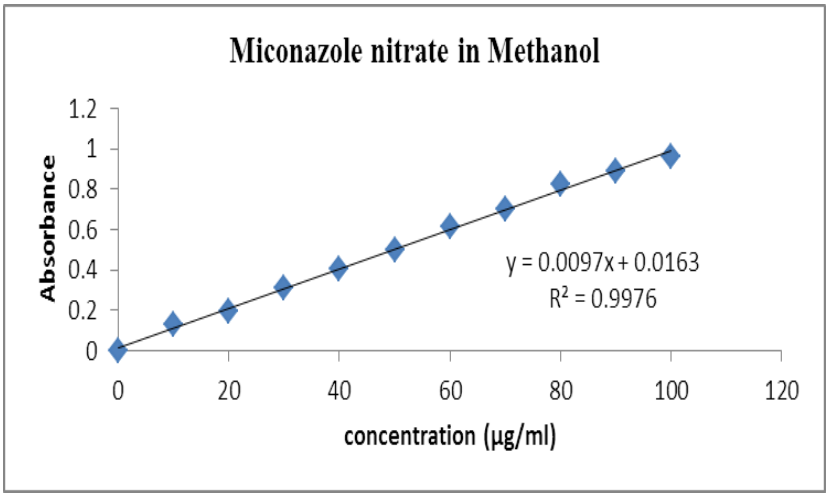

Fig.6: Calibration curve of Miconazole nitrate in Methanol

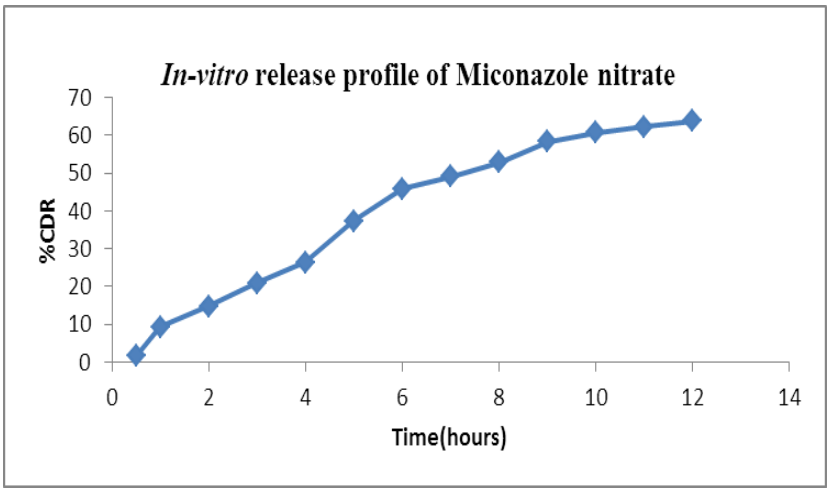

Fig.7:-*In- vitro* Drug Release Profile of Miconazole nitrate

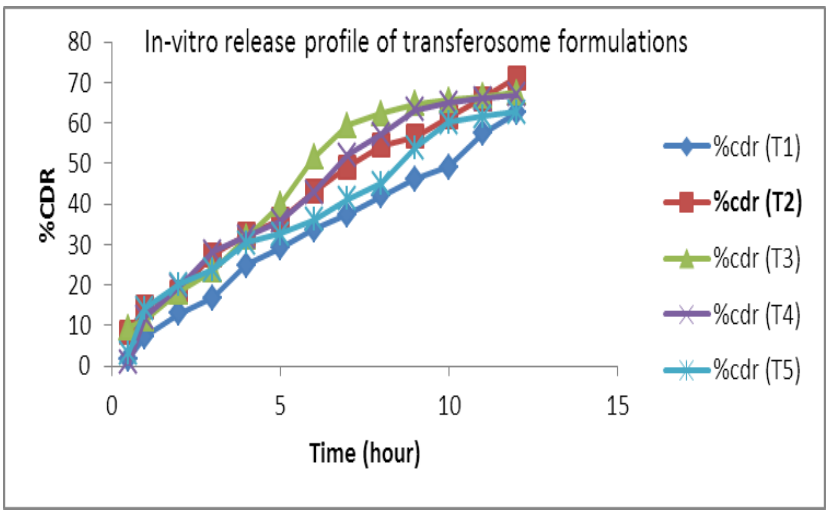

Fig.8:-*In vitro* Drug Release Profile of Formulations (T1-T5)

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