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TOPICAL DRUG DELIVERY OF KETOCONAZOLE ENTRAPPED TRANSFEROSOMAL GEL WITH DESIGN AND ENACTMENT

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ABSTRACT: In pharmaceutical research, the transdermal route of drug delivery has gained great interest, Trasferosomes is a novel vesicular drug carrier system that is composed of water, surfactant, and phospholipids; these were introduced in the early 1990s. The mechanism on which drugs absorb through skin is "osmotic gradient". Transferosomes, when applied on the skin surface it diffuses into skin layers and provides smoothness and hydration to the skin, which facilitates drug absorption. The transferosomal gel of ketoconazole was prepared with the aim to achieve higher diffusion through the skin for the treatment of acne with minimum or no side effects. The formulations were prepared by the reverse-phase evaporation method. Formulations were prepared by varying the ratio of soya lecithin and cholesterol by maintaining room temperature.

INTRODUCTION:

Transferosome: Transferosome is elastic or deformable vesicles, and in the early 1990s they were introduced by "Ceve and hisco-workers". Transdermal delivery has enhanced a novel vesicular drug carrier system called transferosome which is composed of water, surfactant and phospholipid. Transferosome has advantages over other formulations because of their self optimize and ultra-flexible membrane property. The elasticity of the vesicular transferosome is more than the standard liposome therefore well suited for penetration into the skin [1]. Transdermal route for delivery of the drug is a convenient and safer route.

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The vesicular system used in transdermal drug delivery, such as microemulsion, niosomes and liposomes, also which is usually remains confined to the skin surface and do not allow the absorption of the drug effects on the skin [2].

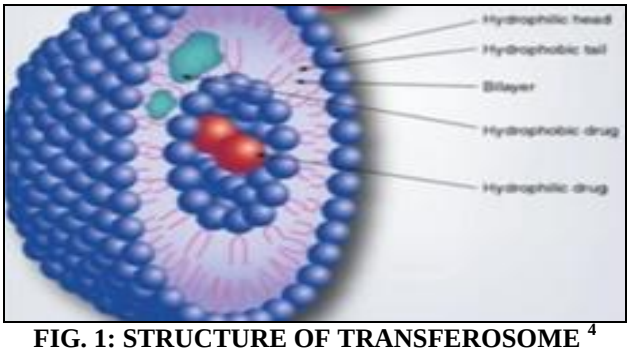

FIG. 1: STRUCTURE OF TRANSFEROSOME [4]

The rational membrane is a concept in which a special type of composite body, so-called trans-ferosome had been developing to overcome the problem of penetration into the skin barriers along with the moisture a gradient of transcutaneous. Transferosome is a recent novel drug delivery

system with a special type of artificial vesicle comprising phosphatidylcholine and edge activator [3].

Mechanism of Penetration of Transferosomes: The mechanism for transferosome diffusion through the skin is "osmotic gradient". Trans-ferosomes cyst diffuses into skin layers and provides smoothness and hydration to the skin which facilitates drug absorption.

The transferosomal gel of ketoconazole was prepared with the aim to achieve higher diffusion through the skin for the treatment of acne with minimum or no side effects. The formulations were prepared by the reverse-phase evaporation method. At room temperature, the ratio of soya lecithin and cholesterol was varied to prepare the formulation of different- different concentrations. During this maximum crucial damage barrier at the stratum corneum diffusion, unpredictable damage of the bilayer is obtained assets; the vesicle principle shows the hydration will be concealed (which should not be arranged properly). The transferosome obligate to accomplish and to found its direction conclude the structure, though it is more considerable to disperse to the skin [5].

MATERIALS AND METHOD:

Material: The drug Ketoconazole from Psychotropics, India limited, ethanol from RFCL Limited, New Delhi (INDIA) Phosphatidylcholine from Sigma-Aldrich Chemical, Mumbai, Cholesterol, chloroform, diethyl ether, Tween 80, span 80, dimethyl sulphoxide from Central drug house (CDH) Pvt. Ltd, New Delhi, India.

Methods:

Preparation of Transferosomes containing Ketoconazole: Transferosomes were prepared by reverse-phase evaporation technique, which requires lipids and surfactant, which aids the formation of an ultra deformable vesicle by using a sonicator. The required amount of soya lecithin and cholesterol were weighed accurately, and tween 80 as surfactant poured in it, and dissolved in a solvent mixture of diethyl ether and chloroform (3:1) and kept at room temperature for 24 h until the thin film formed **Table. 2**. Further added drug solution of ketoconazole, followed by surfactant span 80 and phosphate buffer under sonication. In each solution of transferosomal suspension, dimethyl sulphoxide (DMSO) added as a permeation enhancer [6-8].

Preparation of Topical Transferosomal Gel Formulation: Based on the highest entrapment efficiency, the best formulation was selected for further formulation studies of ketoconazole gel. The gel was prepared using carbopol-934 (1%). The appropriate quantity of carbopol-934 powder was dispersed into distilled water under constant stirring with a glass rod, to avoid formulation of any n dispersible lumps and allowed to hydrate for 24 hr at room temperature for swelling. Topical transferosomal gel formulations were prepared by incorporation of transferosomes containing ketoconazole was mixed into carbopol gel with a mechanical stirrer (50 rpm). The dispersion was neutralized using triethanolamine (0.5% w/w) [9-11].

Optimization of Formulation Parameter and Process Variables: To optimize the dependent variables such as production yield, drug content, and mean particle size of transferosomes, a series of formulation were prepared by varying the concentration of lipid, the effect of surfactant as variables **Table 1** [12].

TABLE 1: OPTIMIZED FORMULA FOR PREPARATION OF TRANSFEROSOMES

Sr. no.	Formulation no.	Phosphatidylcholine	Cholesterol
1	F1	0.3gm	0.1gm
2	F2	0.4 gm	0.2 gm
3	F3	0.5 gm	0.3 gm
4	F4	0.6 gm	0.4 gm
5	F5	0.7 gm	0.5 gm
6	F6	0.8 gm	0.6 gm
7	F7	0.9 gm	0.7 gm
8	F8	1 gm	0.8 gm

Table 1 Represents the formulation by using ingredients in different ratio n = 8

RESULTS AND DISCUSSION:

Physical Appearances of Drug: The drug powder was analyzed for their physical appearances like color; odor, texture and the result shown in **Table 2** [13]. **Table 2** Physical characteristics of ketoconazole.

TABLE 2: PHYSICAL CHARACTERISTICS OF DRUG

1	Color	White to off white
2	Odor	Odorless
3	Texture	Crystalline

Melting Point of Drug: The melting point of the drug was observed by the capillary fusion method. The observed melting value of the drug was the same as the reference value, which describes that the drug was pure. The result is shown in **Table 3**.

TABLE 3: MELTING POINT OF DRUG

Apparatus	Observed value	Reference value
Digital melting point apparatus	150° ± 2.56° C	148°-152°C

Table 3 melting point of the ketoconazole was observed 150° ± 2.56° C.

FTIR Spectroscopy: This infrared spectral assessment of Ketoconazole was carried out for the identification of the drug and was compared with reference IR-spectra given in the IP-2007. After this identification test, it was confirmed that the IR spectral of the drug was the same as that of reference spectra, and also, the drug taken for the preparation of transferosome was pure. IR spectral assessment of Ketoconazole was shown in **Table 4** and IR-spectroscopy results of the drug were shown in the following **Fig. 2**, from here, it was clear that reference spectra and the observed spectra of Ketoconazole were the same as reference, which confirmed the purity of Ketoconazole.

TABLE 4: INTERPRETATION OF INFRARED SPECTRAL OF KETOCONAZOLE

Functional group	Wavenumber observed (cm^{-1})
C=O (Carbonylgroup)	1647.81
C-O (aliphatic ether group)	1032.05
C-O (cyclic ether)	1244.14

Table 4 Interpretation of different functional group of Ketoconazole by using infrared spectroscopy

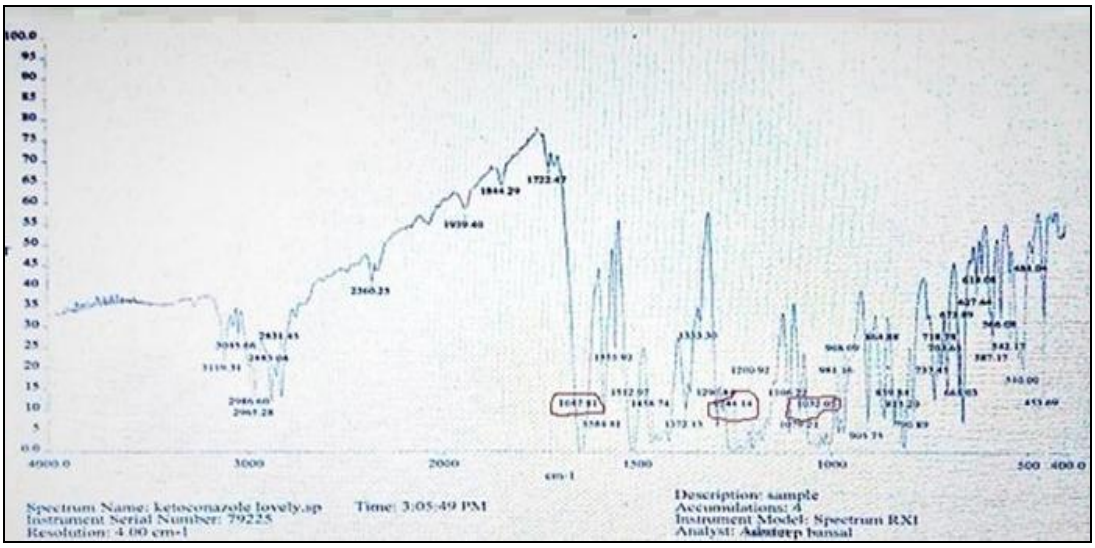

FIG. 2: INTERPRETATION OF FUNCTIONAL GROUP C=O (CARBONYLGROUP) AT 1647.81, C-O (ALIPHATIC ETHER GROUP) AT 1032.05 AND C-O (CYCLIC ETHER) AT 1244.14 OF KETOCONAZOLE BY USING INFRARED SPECTROSCOPY

Chromatographic Study of the Drug: The retention factor (R_f) value is shown in **Table 5**. R_f value found to be close as that of reference value revealed purity of the drug.

TABLE 5: RETARDATION FACTOR (RF) VALUE OF KETOCONAZOLE

Thin-layer chromatography	Retardation factor (Rf) value (observed)	retardation factor (Rf) value (reference)
Ketoconazole	0.73± 0.002	0.70

Table 5 Retardation factor (R_f) observed 0.73± 0.002 of ketoconazole

Calibration Curve: The calibration curve of the ketoconazole was taken in phosphate buffer (pH 7.4).

At different concentrations 0, 5, 10, 15, 20, 25, 30 µg/ml, the absorbance of the drug was analyzed by ultraviolet (UV) spectrophotometer. The calibration curve data is shown in **Table 6**.

A graph **Fig. 3** was plotted between concentration and time. The Regression coefficient was calculated as R2=0.9994, which indicated the linearity of graph [14].

TABLE 6: CALIBRATION CURVE DATA OF KETOCONAZOLE

Sr. no	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.225±0.0021
3	10	0.428±0.0032
4	15	0.639±0.0014
5	20	0.826±0.0016
6	25	1.063±0.0017
7	30	1.280±0.0023

Table 6 Represents the absorbance of different concentration (n=7)

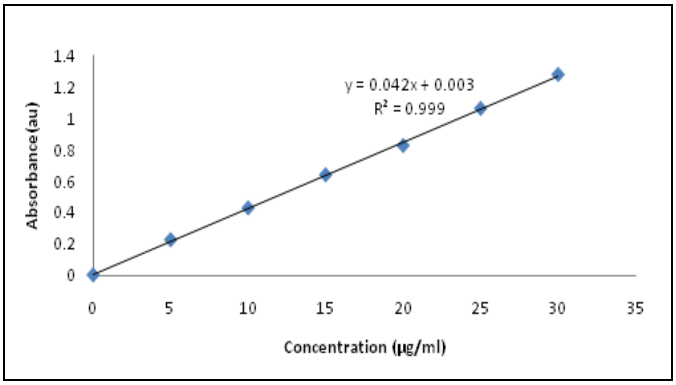

FIG. 3: SEVEN POINT CALIBRATION PLOT OF KETOCONAZOLE AT 244NM WAVELENGTH IN PHOSPHATE BUFFER (PH 7.4)

Equilibrium Solubility Study of Drug: The equilibrium solubility of the drug done for 72 h with 25 ml phosphate buffer (pH 7.4), and the solubility of the drug found to be 0.591±0.007 **Table 7** [15].

TABLE: 7 SOLUBILITY OF KETOCONAZOLE

Solvent	Solubility (mg/ml)
Phosphate buffer (pH 7.4)	0.591± 0.007

Table 7 Solubility of ketoconazole observed 0.591± 0.007.

Preparation and Evaluation of Ketoconazole Loaded Transferosomes: Eight formulations of ketoconazole transferosomes were successfully prepared by altering the ratio of lipids using the reverse phase evaporation technique. The developed formulations were evaluated for different parameters, which are as follows:

Entrapment Efficiency: The entrapment efficiency of the different formulation is determined by the method given in the material and method section. The entrapment efficiency of the different formulation is shown in **Table 9** and the production yield are shown in **Table 8**. The entrapment efficiency of all formulation found to be in the range of 48.90 to 63.44% [16].

TABLE 8: ENTRAPMENT EFFICIENCY OF DIFFERENT TRANSFEROSOMES PREPARATION (F1-F8)

Formulation Code	Entrapment efficiency (%)
F1	59.93±1.52
F2	48.90±0.85
F3	54.70±2.49
F4	52.24±1.78
F5	57.39±0.63
F6	50.57±1.96
F7	63.44±2.04
F8	52.82±1.15

Table 8 Entrapment efficiency of ketoconazole transferosome (n=8)

TABLE 9: PRODUCTION YIELD OF DIFFERENT TRANSFEROSOMES PREPARATION (F1-F8)

Formulation Code	Production Yield
F1	81.45±2.17
F2	79.83±1.05
F3	82.02±1.33
F4	77.50±3.61
F5	75.78±1.42
F6	74.61±3.08
F7	76.22±1.62
F8	72.88±2.97

Table 9 Production Yield of ketoconazole transferosome (n=8)

Determination of Particle Size Shape and Morphology: The morphology of the optimized transferosome (F7) was investigated by TEM. The TEM photographs of transferosomes are shown in **Fig. 4**. It was observed by Transmission electron microscopy (TEM) analysis that the optimized transferosomes were spherical in shape. Particle size was determined by using Malvern zeta sizer, and the results are shown in **Fig. 5**.

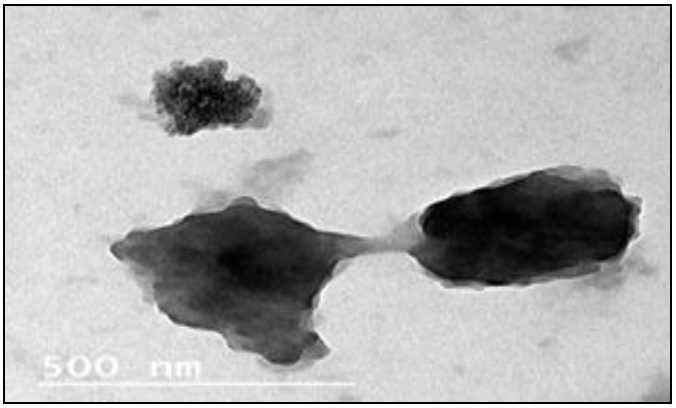

FIG. 4: TEM OF (F7) TRANSFEROSOMES

***In-vitro* Drug Release Studies:** *In-vitro* dissolution studies for all the formulated transferosomes were carried out using the united state pharmacopoeia (USP) paddle method. Results are shown in **Table 10** and **Fig. 4**. The maximum release found to be 75.85 ± 1.18 of best Transferosomes formulation.

TABLE 10: *IN-VITRO* DRUG RELEASE OF KETOCONAZOLE TRANSFEROSOMES FORMULATIONS

Time (min)	% cumulative drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	19.96±0.52	17.13±1.13	19.06±1.03	19.65±1.58	17.18±1.27	18.83±1.60	22.35±0.40	19.36±0.80
2	27.63±1.16	24.48±1.54	27.15±1.29	26.11±1.02	29.54±1.70	27.52±1.66	29.52±1.33	34.04±0.24
3	36.48±1.53	39.41±2.50	35.87±1.57	33.65±1.92	37.56±1.49	36.84±1.73	38.47±1.28	42.93±0.27
4	46.92±1.20	44.32±1.35	41.28±1.50	41.74±1.19	44.54±1.73	39.68±1.43	48.92±1.63	51.41±0.56
6	58.66±1.51	50.91±1.18	49.86±1.89	48.92±1.52	47.55±1.58	42.63±1.02	59.45±0.28	52.45±0.91
8	64.21±1.44	57.54±1.40	54.64±1.31	52.63±1.85	51.36±1.97	49.36±1.50	65.69±0.37	57.56±0.90
10	68.52±1.51	62.52±1.74	60.87±1.09	59.32±1.42	56.21±1.38	53.96±1.66	69.12±1.11	59.38±1.13
12	72.62±1.48	67.25±1.29	64.65±1.58	63.65±1.21	62.85±1.03	59.85±1.74	75.85±1.18	67.38±1.15

Table 10 *In-vitro* drug release of ketoconazole Transferosomes formulations (n=8)

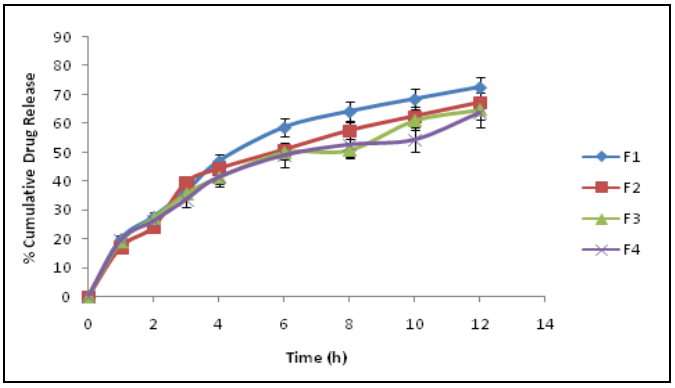

FIG. 5: *IN-VITRO* DRUG RELEASE OF KETOCONAZOLE TRANSFEROSOME FORMULATIONS (F1-F4)

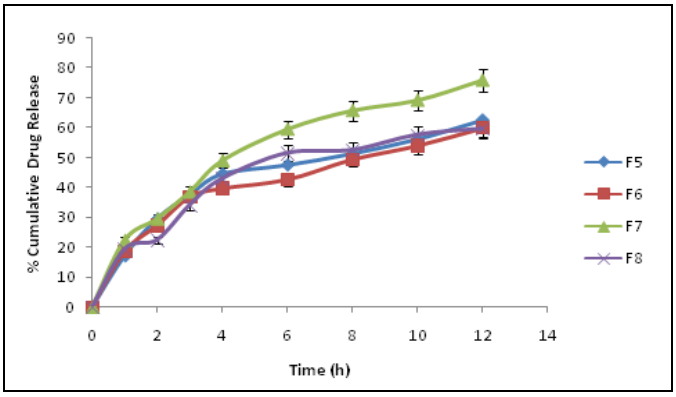

FIG. 6: *IN-VITRO* DRUG RELEASE OF TRANSFEROSOME FORMULATIONS (F5-F8)

Kinetic Assessment of Ketoconazole loaded Transferosomes: Different release kinetics models were applied on the data of best formulation of transferosomes shown **Table 11** and the best fit model found to be Higuchi which suggested diffusion as a mechanism of release [17].

TABLE 11: KINETIC ASSESSMENT OF KETOCONAZOLE LOADED TRANSFEROSOMES

Formulation code	Zero odor (R2)	First odor (R2	Higuchi type (R2)	Korsmeyer pepper Release
F7	0.8837	0.9012	0.986	0.970

Table 11 Kinetic assessment of ketoconazole loaded transferosome (n=1)

We have prepared no. of formulation by using different ratio of Phosphatidylcholine and cholesterol out of which formulation (F7) was better than other due to its better entrapment efficiency, TEM and as well as percentage of drug release.

Evaluation of Transferosomes loaded Carbopol-940 gel:

(Pouvoir hydrogene) pH: A digital pH meter was used to measure the Pouvoir hydrogene (pH) of Transferosomes gel. Reading was taken thrice. The pH of Transferosome gel best formulation was found to be 7.0±0.09 indicates neutral Pouvoir hydrogene (pH).

Appearance: The prepared transferosome gel was inspected visually for clarity, color, and the presence of any particle. Transferoasome loaded gel best formulation was found to be transparent and no particle was found in that.

Spreadability: Spreadability is a term express to denote the extent area to which the gel readily spread on application to the skin or affects part found to be 254.56 $gmcm^2$/ sec [18].

Consistency: The measurement of the consistency of the prepared gel was done by dropping a cone attached to a holding rod from a fixed distance of 10 cm in such a way that it should fall on the center of the glass cup filled with the gel. The consistency of the best formulation was found to be optimum.

Homogeneity: The prepared transferosome gel was evaluated visually for homogeneity, and it was found to be homogeneous.

***In-vitro* Diffusion Study:** *In-vitro* diffusion study carried out by using Franz diffusion cell using phosphate buffer (pH 7.4) as dissolution medium, and the percent drug diffused found to be 72.15±1.49 after 12 h Results shown in **Table 12** and **Fig. 7** [19].

TABLE 12: *IN-VITRO* DIFFUSION STUDY OF TRANSFEROSOMES GEL FORMULATION (F7)

Time (h)	% Drug Diffused
0	0
1	17.23±0.57
2	20.19±1.17
3	24.31±1.89
4	30.46±0.82
5	41.41±1.65
6	45.74±1.44
7	47.80±2.19
8	50.49±1.04
9	62.41±1.96
10	65.63±1.34
11	70.22±2.70
12	72.15±1.49

Table 12 *In-vitro* diffusion study of Trans-ferosomes gel formulation (n=1)

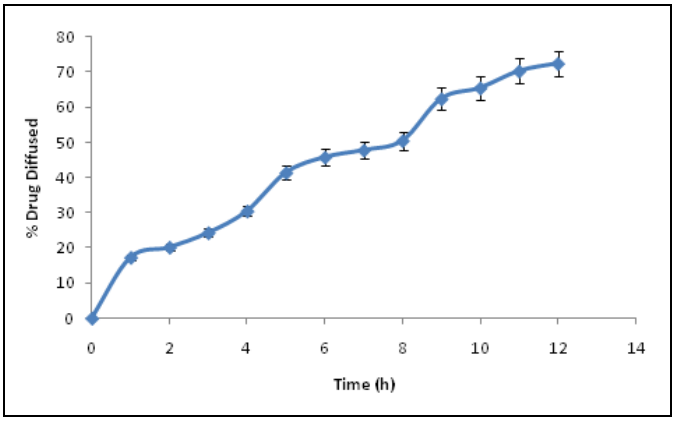

FIG. 7: *IN-VITRO* DIFFUSION STUDY OF TRANS-FEROSOME GEL (F7) FORMULATION

CONCLUSION: Transferosomal gel of ketoconazole was successfully prepared and evaluated for different parameters. The developed transferosomes were found to possess good entrapment efficiency and high production yield. In-vitro drug release of different formulations was calculated and the best formulation in terms of % cumulative drug release (CDR) was obtained. The best formulation was formulated as carbopol gel which showed good spreadability, consistency, homogeneity, and in-vitro diffusion study. Finally, based on results, we can conclude that Ketoconazole entrapped transferosomes gel showed satisfactory results, so the transferosomal gel of ketoconazole can be used for the treatment of acne as the drug can diffuse dipper in the skin.

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