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Development and characterization of miconazole nitrate transfersomal gel

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ABSTRACT

Miconazole nitrate (MIC) is an antifungal drug used for treatment of superficial fungal infections. However, it has low skin permeability. Hence, the basic idea behind the development of such a system, transfersomes is to maintain a sustain release of drug from the dosage form and for target delivery. Miconazole nitrate was formulated as transfersomes, half-life can be increased and the desired effect can be obtained. MIC transfersomes were prepared using a thin lipid film hydration technique. The prepared transfersomes were evaluated with respect to entrapment efficiency (EE%), particle size, and quantity of *in vitro* drug released to obtain an optimized formulation. The optimized formulation of MIC transfersomes was incorporated into a Carbapol 934 gel base which was for drug content, pH, spreadability, viscosity, *in vitro* permeation, and *in vitro* activity. The prepared MIC transfersomes had a high EE% ranging from 65.45% to 80.11%, with small particle sizes ranging from 368 nm to 931 nm. The *in vitro* release study suggested that there was an inverse relationship between EE% and *in vitro* release. In 24 hrs the drug release was observed ranging from 79.08% to 88.72%. The kinetic analysis of all release profiles was found to follow Higuchi's diffusion model. All independent variables had a significant effect on the dependent variables (p-values < 0.05). Therefore, Miconazole nitrate in the form of transfersomes has the ability to penetrate the skin, overcoming the stratum corneum barrier. When the data subjected to zero order and first order kinetics model, a linear relationship was observed with high R2 values for zero order model as compared to first order model and suggested that the formulations followed zero order sustained release.

Keywords: Antifungal activity; Carbapol 934; Entrapment efficiency; Miconazole nitrate; Transfersomes.

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INTRODUCTION

Miconazole topical is an antifungal medication. Miconazole topical prevents fungus from growing on your skin. Miconazole topical (for the skin) is used to treat skin infections such as athlete's foot, jock itch, ringworm, tinea versicolor (a fungus that discolors the skin), and yeast infections of the skin. Miconazole topical may also be used for purposes not listed in this medication guide. The antifungal agent used topically often in its nitrate form, to treat candidiasis and other fungal infections is known as Miconazole nitrate.[1]

The development of a new drug delivery system has been of great interest. The purpose of the novel drug delivery system is to deliver the drug to the body's needs during the treatment cycle and to redirect the active agent to the action site. There have been a number of new drug delivery systems which cover many administrative routes to ensure managed and targeted distribution. One such method is the encapsulation of a drug in vesicular structures, which could be expected to extend the life of the drug in systemic circulation and minimize toxicity if the drug can be chosen. A variety of vesicular systems have therefore been developed for the delivery of drugs, such as liposomes, niosomes, pharmacosomes and transfersomes. The use of liposomal, transfersome vesicular systems, as well as the ability to integrate hydrophilic and lipophilic medicines are one of the options for improving the penetration of drugs in the skin.

Recent strategies in drug delivery include distributing the medication at a default rate known as the controlled release delivery system. Such devices also helped to reduce the side-effects of the conventional

multidose therapy program. Due to the various advantages this administration route provides, the production of transdermal dosage forms has been attracting growing attention in recent years. Transdermal delivery system generally shows better regulation of blood levels, decreased occurrence of systemic toxicity, no first-pass hepatic metabolism, and higher compliance as compared with conventional formulations. Transdermal treatment systems are characterized as self-containing and discrete dosage types, which supply the medication with a regulated rate of systemic circulation through the skin if applied to the intact skin.[2]

The medication system provides a range of potential benefits over traditional routes, such as the prevention of first-pass metabolism, predictable and extended activity, short-term use of medicines, improved physiological or drug responses, a reduction in negative side-effects, avoided fluctuations in drugs levels, inter-patient and intra-patient variations and, most importantly, minimized adverse effects.[3] A variety of methods in the field of medical research have been used to improve the effectiveness of material across to intact skin using penetrators, enhancers, ionotophoresis, sonophoresis and vesicular constructions. The word "vesicular constructs" is used with liposomes, niosomes, virosomes, ethosomes and transfersomes.[4]

Transfersomes were designed to benefit from phospholipid vesicles as a transdermal medication's carrier. Transferosomes overcome the problem of skin penetration by rubbing the intracellular lipid of the corneum of the stratum. Due to the high deformation of the vesicle, this is possible due to the external mechanical stress. This enables entry in a self-adjusting manner. The resulting flexibility in the Transfersomes membrane reduces the risk that the skin will be rupture completely and allows transfersomes to follow the natural water gradient in a non-occluding condition throughout the epidermis.[5] The Transfersomes can spontaneously penetrate the intact stratum corneum via two intracellular, bilayer-variable lipid pathways.

Transfersomes, a new class of modified liposomes were derived from the Latin word "transfer", And the Greek word "soma" meaning "a body. "Transfersomes, which are initially reported by Cevc[6] and are different descriptions of deforming, highly-deformable, elastic or ultra-flexible liposomes are claimed to improve transdermal, *in vitro* delivery of a wide range of drugs and are defined as non-natural vesicular designed to display an attribute of cell vesicle or cell engaged in exocytosis.[7] The deformation of transferosomes is the result of integration of the edge activator into the bilayer phospholipids which increases elasticity through the destabilization of lipid bilayers.[8] Edge activators are commonly used as single-chain surfactants such as sodium cholate and tween 80.[9,10] Transfersomes will squeeze around one-tenth of the diameter of the vesicles through conduits and allow them to spontaneously enter the stratum corneum.[11]

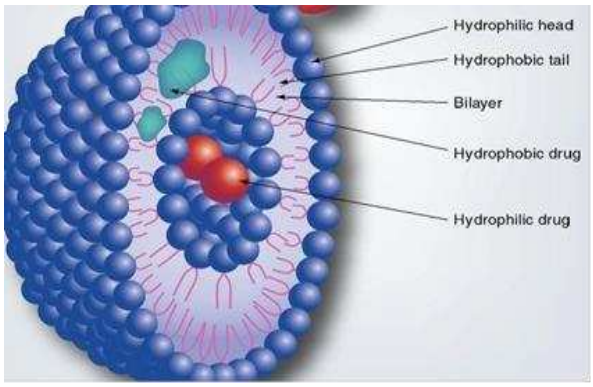

Figure 1: Structure of Transfersomes[13]

MATERIALS AND METHODS

Materials

Miconazole Nitrate was obtained as a gift sample from vital Laboratories Pvt. Ltd, soya lecithin was purchased from Himedia, and methanol was purchased from Fischer Scientifics, Span 80 and tween 80 was procured from Reachem, Mumbai., India and Carbopol 934 was procured from Loba Chamoe Pvt Ltd, Mumbai

Preparation of Miconazole nitrate Loaded Transfersomes

Soya-phosphatidylcholine was taken in a round bottom flask. Span80 (sp) or Tween 80 (Tw) was put in the same round bottom flask. Methanol was then added to the same flask. The Miconazole nitrate was also loaded in the same RBF. These were then dissolved by shaking. Thin film was then formed by keeping it in the rotatory vacuum evaporator at 60^0C. To prepare small vesicles, resulting LMVs were sonicated at room temperature or 500C for 30min. the sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100nm polycarbonate membrane. Then finally we got the Transferosome were transferred to 2% w/v carbopol gel.

Preparation of Gels

Preparation of carbopol gel base: 0.5 g Carbopol 934 was weighed and dispersed in water with mild stirring and allowed to swell for 24 hours to obtain 0.5% gel. Later 2 ml of glycerin was added to for gel consistency. As shown in the (Table 1) different compositions of Carbopol 0.5, 1 and 2% gels were prepared.[12]

Table 1: Composition of different gel base

Formulation	Carbopol (%)
TF1	0.5
TF2	1.0
TF3	2.0

Table 2: Formulation chart of Miconazole nitrate loaded transferosomal gel

Formulation Code	Composition					
	Drug (mg)	Lecithin (mg)	Span80 (mg)	Tween80 (mg)	Methanol (ml)	Phosphate buffer (ml)
F1	10	95	5	-	2	10
F2	10	90	10	-	2	10
F3	10	85	15	-	2	10
F4	10	80	20	-	2	10
F5	10	75	25	-	2	10
F6	10	70	30	-	2	10
F7	10	95	-	5	2	10
F8	10	90	-	10	2	10
F9	10	85	-	15	2	10
F10	10	80	-	20	2	10
F11	10	75	-	25	2	10
F12	10	70	-	30	2	10

Evaluation of miconazole nitrate transfersomes

Drug- Excipient Compatibility

Differential scanning Calorimetry (D.S.C): Differential Scanning Calorimetry (DSC) is used to check the compatibility of drug with excipients. DSC measurements were done on pyris calorimeter. Approximately 3-5mg of drug were weighed accurately a into standard aluminum pan. An empty pan was used as a reference. The samples were heated from room temperature to 390°C with scan rates 10°c/minute. Then the DSC curves are recorded with the help of computer scans. [14]

Fourier transforms infrared spectroscopy (FT-IR): FTIR spectroscopy was carried out to check the compatibility between the drug and polymer. The IR spectra of Miconazole Nitrate and physical mixtures of drug and polymer was carried out by using FTIR, Bruker. The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. The wave numbers of characteristic peaks of physical mixtures were compared with the pure samples and interpreted. [15]

Vesicle morphology: For SEM one drop of Transfersomes were mounted on the stab covered with clean glass and coated with gold and were observed under the scanning electron microscope at an accelerating voltage of 20KV and photomicrographs of suitable magnification was obtained.

Particle size: Size was determined using a Zetasizer 300HS. Samples were diluted with distilled water and measured at a temperature of 25°C. The diameter was calculated from the autocorrelation function of intensity of light scattering from transferosomes. [16]

Drug content: 1gm each formulation containing approximately 40mg of drug was taken in a 50 ml volumetric flask and diluted with methanol and shaken to dissolve the drug in methanol. The solution was filtered through Whatmann filter paper, 0.1 ml of the filtrate was pipette out and diluted 10ml of methanol. The content of the drug was observed in UV-Spectrophotometer. [17, 18]

Entrapment Efficiency: The concentration of Miconazole nitrate in the formulation was determined by UV analysis after disruption of the vesicles with Triton X-100 (0.5% w/w). The vesicle/Triton X-100 solution was centrifuged at 10,000 rpm at 4^0C for 10 min. The supernatant was filtered. The entrapment efficiencies and the loading efficiencies of the Miconazole nitrate-loaded formulation were calculated by UV. [19]

$$\text{Entrapment efficiency} = \left(\frac{\text{Amount entrapped}}{\text{Total amount added}}\right) \times 100$$

***In vitro* drug release studies**

The *in vitro* permeation behaviour of Miconazole nitrate from all transfersomal gel formulations and the control gel formulation (containing drug, span 80, Tween 80, and Soya phosphatidylcholine) were investigated using cellophane membrane (Molecular weight cut of 12000–14000). The vertical type of the Franz Diffusion cell was designed, fabricated, and validated prior to the permeation study. The cellophane membrane was mounted on a diffusion cell assembly with an effective diffusion area of 2.303 cm^2. The receptor compartment consisted of a 22.5 ml phosphate buffer at pH 7.4 as the receptor fluid agitated at 100 rpm, and was maintained at 37 ± 0.5°C throughout the experiments. The prepared formulation was applied to the membrane in the donor compartment. An aliquot of 2 mL sample was withdrawn at suitable time intervals and replaced immediately with an equal volume of fresh diffusion medium. The cumulative amount that permeated across the cellophane membrane was calculated and plotted against time. [20, 21]

Kinetics of drug release: To examine the drug release kinetics and mechanism the cumulative release data were fitted to models of data treatment as follows:

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)

- Cumulative percentage drug release Vs. SQRT (Higuchis classical diffusion equation)
- Log of cumulative percentage drug release Vs. log time (Peppa's exponential equation).

RESULTS AND DISCUSSION

A successful attempt was made formulate transferosomes gel of Miconazole nitrate using different surfactants. Effect of surfactant applied on formulations was assessed. In the present work, twelve formulations were prepared and composition is mentioned in table. Among these one of the best formulations was loaded into carbopol gel. The formulated transferosomes and gel were characterized for various physicochemical parameters.

Preformulation studies of pure drug:

Drug excipients compatibility studies

Chemical compatibility-Differential scanning calorimetry (DSC) studies: The DSC procedure is followed and DSC thermogram of API, drug-Excipient compatibility blend were shown in the (Figure 2 and Figure 3).

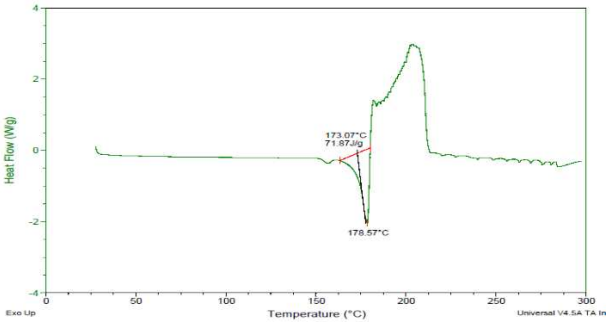

Figure 2: DSC Thermogram of Miconazole Nitrate (API)

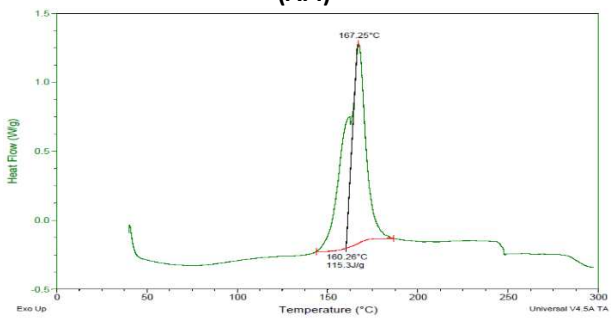

Figure 3: DSC Thermogram of Miconazole Nitrate (API) + Excipient

Identification of Miconazole nitrate: The IR spectrum of pure drug was found to be similar to that of standard spectrum of Miconazole nitrate. The spectrum of Miconazole nitrate shows the following groups at their frequencies shown in 1473, 1642, 2904, 3407 cm-1. Determination of melting point. The melting point of Miconazole nitrate was found to be 170-184°C which complied with the BP standards. Drug-polymer compatibility: Compatibility studies of pure drug Miconazole nitrate with polymers were carried out prior formulation of transferosomes. IR spectra of pure drug and polymer were taken. All the characteristic peaks of Miconazole nitrate were present in spectra at respective wavelength. As shown in (Figure 4, Figure 5, Figure 6, Figure 7) Thus, indicating compatibility between drug and polymers were interpretation was represented in (Table 3) and It shows that there was no significant change in the chemical integrity of the drug.

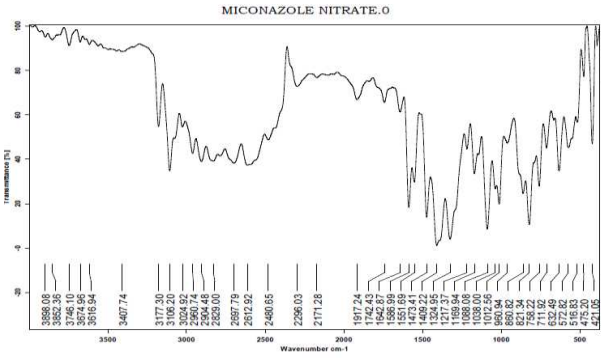

Figure 4: FTIR of Miconazole nitrate drug

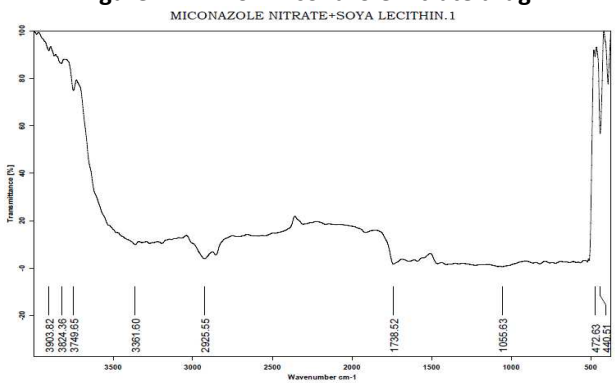

Figure 5: FTIR of Miconazole nitrate+ Soya Lecithin

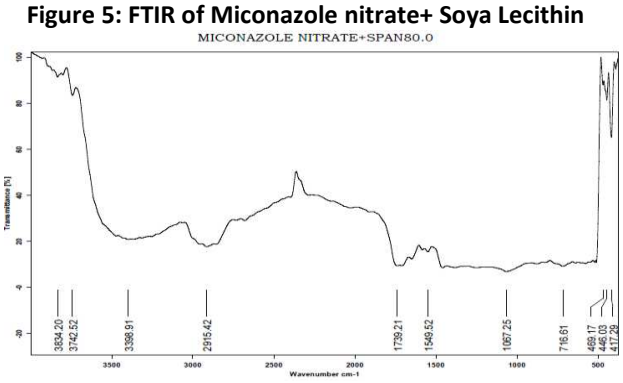

Figure 6: FTIR spectra of Pure Miconazole nitrate + Span 80

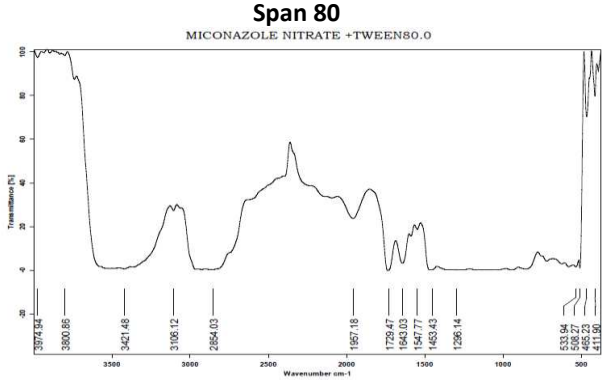

Figure 7: FTIR spectra of Pure Miconazole nitrate + Tween 80

Table 3: Interpretation of Miconazole nitrate and physical mixtures

S.no	Type of bond	Type of stretch	IR absorption bands (cm^{-1})			
			Characteristic peak	Pure Drug (Miconazole Nitrate)	Physical Mixture (drug + span80 + soya lecithin)	Physical Mixture (drug + tween80 + soya lecithin)
1	N-H	Stretch	3500-3300	3407.74	3361.60	3398.91
2	C-H	Stretch	2960-2850	2904.48	2925.55	2915.42
3	C=O	Stretch	1600-1900	1642.87	1738.52	1739.21
4	C-C	Stretch	1450-1070	1473.41	1055.63	1067.25

Morphology: The prepared transferosomes were undergone morphological studies by using optical microscopic method. Small quantity of sample spreaded over clean slide. The slide was focused under optical light and images were snapped by using optical microscopy attached with Dewinter Microscopic camera software. According to morphological evaluation analysis, all vesicles types seemed to have a spherical or oval shaped which had been resulted or shown in (Figure 8). These oval-shaped vesicles may have resulted from the transferosomes' deformation, which might occur during the sample preparation.

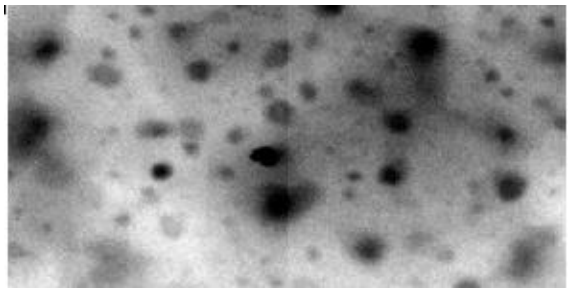

Figure 8: SEM image of transferosomes

Particle size: Particle size analysis showed that the sizes of different formulations were in the range of 368 nm and 931 nm indicating that these vesicles were all of a small size. From formulation F1 to F12 particle size are listed in (Table 4)

Drug content: Drug content uniformity was determined as triplicate by dissolving in methanol and dissolved transferosomes were undergone centrifugation at 3000rpm for 2hrs and filtered with Whatmann filter paper (0.45,) Whatman, Maidstone, UK). The solution was diluted to Beer's range and observed in UV-Spectrophotometer). The value range from 80.45% to 94.15% as shown in (Table 4).

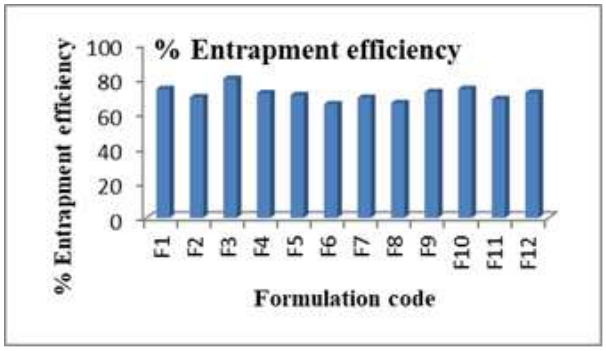

Figure 9: Entrapment Efficiency of F1 to F12 Formulations

Entrapment Efficiency

The entrapment efficiency of deformable vesicles formulations were found to be in the range of 66.12 to 80.11. The percentage entrapment efficiency for span80 was maximum F3 for i.e. 80.11 and minimum for F6 i.e. 65.41 and in case of tween80 maximum for F10 i.e. 74.25 and minimum for F8 i.e. 66.12%. as shown in (Figure 9).

Table 4: Particle size, Entrapment Efficiency of F1 to F12 Formulations

S. No	Formulation Code	Particle size (nm)	Drug content (%)	Entrapment Efficiency (%)
1	F1	620	87.65	74.14
2	F2	741	81.43	69.42
3	F3	368	88.91	80.11
4	F4	721	90.31	71.78
5	F5	866	87.41	70.65
6	F6	871	94.15	65.41
7	F7	644	83.46	69.12
8	F8	702	80.45	66.12
9	F9	794	89.14	72.44
10	F10	462	85.16	74.25
11	F11	866	84.25	68.36
12	F12	931	88.16	72.11

***In vitro* Diffusion Studies**

In vitro diffusion studies of all the formulation of transferosomes of Miconazole nitrate were carried out in pH 7.4 phosphate buffer. The study was performed for 24hrs and cumulative percentage drug release was calculated at different time intervals. The *in vitro* drug release profile for the formulation (F1 to F6), (F7 to F12) were tabulated in (Table 5 and Table 6) . The plot of time Vs cumulative % drug release formulations (F1 to F6) to (F7 to F12) were plotted and depicted in (Figure 10 and Figure 11)figures. Effects of various surfactants and their concentration on drug release were studied.

***In vitro* drug release studies from gel through a cellophane membrane:**

Transferosomal gel formulation was subjected to *in vitro* drug release studies using a cellophane membrane. The cumulative amount of drug release was calculated. Results revealed that highest cumulative amount of drug release 88.62% up to 24hrs.

Table 5: *In vitro* percentage Cumulative drug release of F1 to F6

S.No	Time (Hrs)	% Cumulative drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	12.54±0.02	13.50±0.48	16.87±0.09	13.27±0.25	11.44±0.12	11.68±0.01
3	2	20.66±0.22	16.09±0.25	20.41±0.24	23.36±0.31	27.57±0.25	23.48±0.05
4	3	29.99±0.35	20.82±0.43	23.99±0.26	26.91±0.16	30.13±0.19	27.96±0.09
5	4	32.57±0.02	29.01±0.38	27.60±0.06	31.60±0.09	37.29±0.24	34.61±0.1
6	5	39.73±0.12	32.72±0.27	33.49±0.09	35.22±0.13	42.23±0.35	39.20±0.33
7	6	41.26±0.28	38.74±0.36	38.31±0.35	39.99±0.38	46.08±0.29	42.77±0.42
8	7	48.51±0.24	44.82±0.25	45.43±0.24	42.59±0.46	48.81±0.31	45.31±0.21
9	8	51.26±0.32	50.96±0.34	51.50±0.29	50.74±0.24	52.71±0.19	48.93±0.32
10	12	64.30±0.15	60.58±0.09	60.99±0.32	61.18±0.5	62.37±0.41	57.89±0.44
11	24	82.03±0.27	81.69±0.19	79.57±0.45	87.21±0.19	85.84±0.22	81.81±0.49

Table 6: *In vitro* percentage Cumulative drug release of F7 to F12

S.No	Time (Hrs)	% Cumulative drug release					
		F7	F8	F9	F10	F11	F12
1	0	0	0	0	0	0	0
2	1	16.77±0.15	19.88±0.09	15.70±0.09	21.13±0.09	13.05±0.1	19.28±0.16
3	2	31.32±0.18	28.78±0.1	20.35±0.12	24.87±0.06	17.93±0.16	24.01±0.19
4	3	32.83±0.26	34.04±0.14	27.28±0.19	28.64±0.12	25.23±0.24	28.78±0.1
5	4	37.94±0.33	39.35±0.24	32.03±0.24	33.61±0.17	30.23±0.32	35.87±0.24
6	5	41.91±0.28	42.22±0.35	40.20±0.31	42.16±0.21	32.90±0.19	44.16±0.29
7	6	48.31±0.39	50.09±0.29	45.08±0.22	46.10±0.26	39.15±0.25	49.13±0.22
8	7	51.17±0.45	53.06±0.14	47.76±0.29	47.72±0.32	47.84±0.35	53.01±0.34
9	8	60.05±0.42	63.51±0.32	51.59±0.24	54.05±0.41	51.86±0.12	56.93±0.19
10	12	71.41±0.46	74.07±0.28	62.18±0.45	65.13±0.34	63.05±0.25	65.41±0.45
11	24	87.67±0.49	88.45±0.26	82.97±0.24	83.37±0.45	79.08±0.29	88.72±0.49

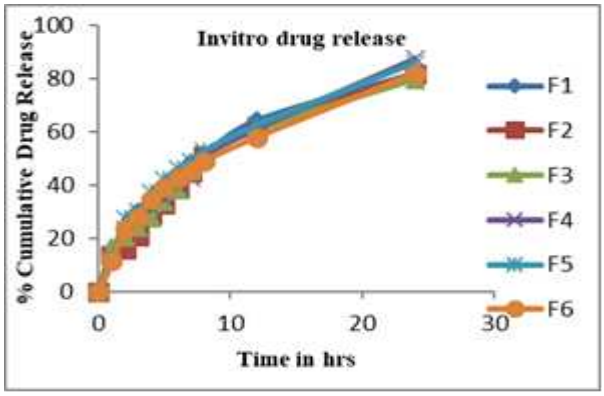

Figure 10: In-vitro Diffusion studies for F1 to F6

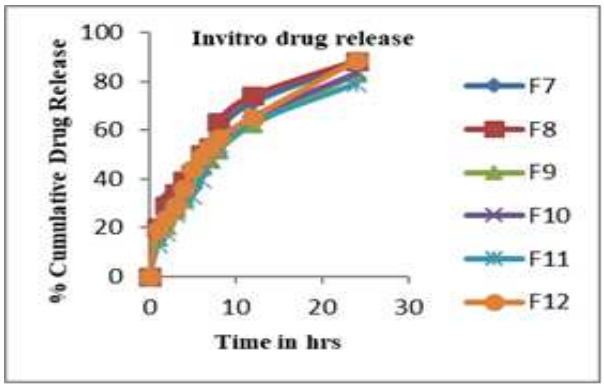

Figure 11: In-vitro diffusion studies for F7 to F12

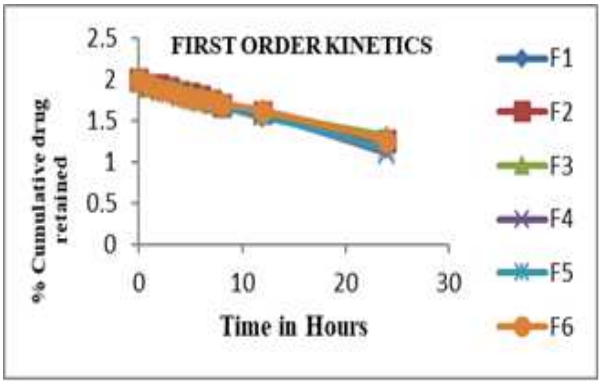

Figure 12: Time Vs Drug retained (First order kinetics) of formulations F1 to F6

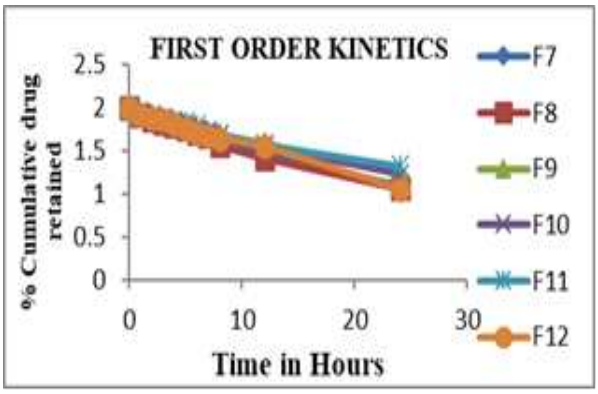

Figure 13: Time Vs Drug retained (First order kinetics) of formulations F7 to F12

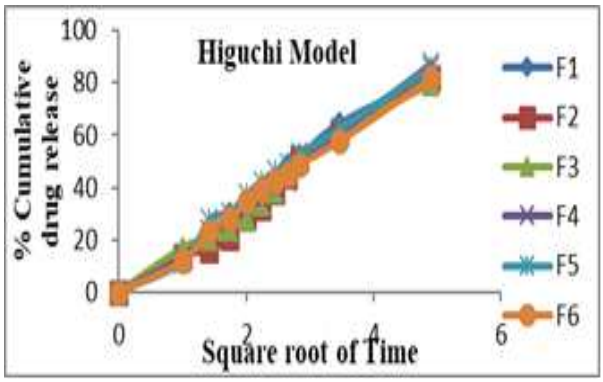

Figure 14: Square root of Time Vs % Cumulative Drug Released (Higuchi Release mechanism) of Formulation F1 to F6

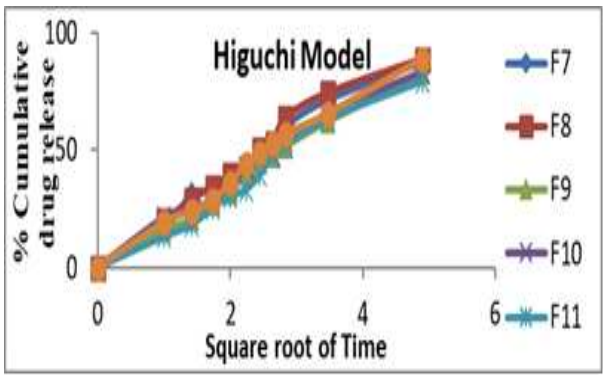

Figure 15: Square root of Time Vs % Cumulative Drug Released (Higuchi Release mechanism) of Formulation F7 to F12

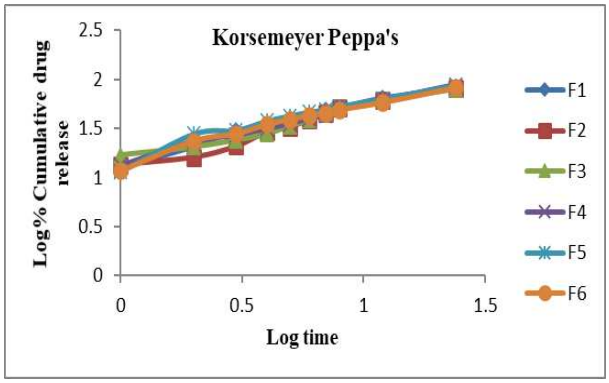

Figure 16: Log Time Vs Cumulative % Drug Released (Korsmeyer-Peppas Release Mechanism) of Formulations F1 to F6

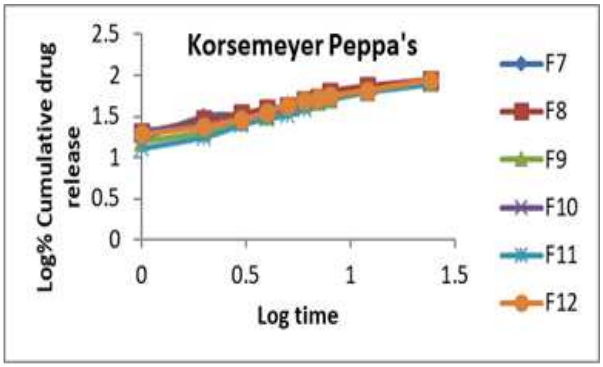

Figure 17: Log Time Vs Cumulative % Drug Released (Korsmeyer-Peppas Release Mechanism) of Formulations F7 to F12

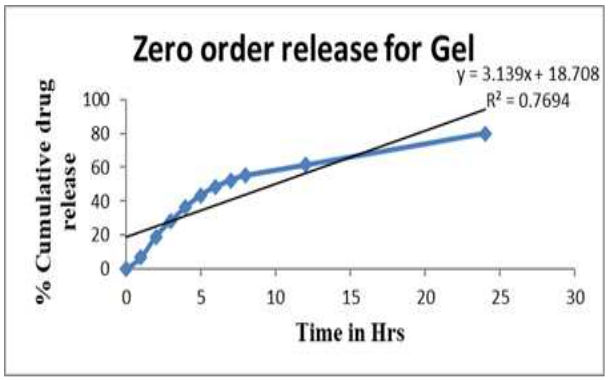

Figure 18: Time Vs % Cumulative drug release (Zero order kinetics) of F3 Formulation Gel

SUMMARY

Miconazole nitrate is mainly used in the treatment of fungal infections. The basic idea behind the development of such a system is to maintain a sustain release of drug from the dosage form and for target delivery. In the research work an attempt was made to formulate and evaluated the transferosomal gel for sustained effect. The drug excipient compatibility studies were carried out by using DSC & FT-IR technique. Based on the results, excipients were found to be compatible with Miconazole nitrate. In preformulation study, estimation of Miconazole nitrate was carried out by U.V spectrophotometer at λ max 272 nm using water as solvent, which had a good reproducibility and this method was used entire study. Entrapment efficiency ranging from 65.45 to 80.11% was obtained. Particle size of transferosomes was found to be in the range of 368 to 931 nm. In 24 hrs the drug release was observed ranging from 79.57% to 88.72%. Drug release from the gel was observed that 79.57%. In order to reduce the probable mechanism of drug from the dosage form, the result of *in vitro* dissolution studies were fitted to various kinetics equations. When the data subjected to zero order and first order kinetics model, a linear relationship was observed with high R^2 values for zero order model as compared to first order model and suggested that the formulations followed zero order sustained release.

CONCLUSION

Transferosomal drug delivery system offers a simple and practical approach to achieved increase bioavailability, avoids first pass metabolism and modify drug release profiles essential for sustained, site specific and localized drug action. *In vitro* release obeyed zero order kinetics with mechanism of release zero order followed by non fickian diffusion due to more lipophilic nature of polymers used. The drug permeation was slow and study and 79.57% of Miconazole nitrate could permeate through the skin into the pilosebaceous unit in 24hrs. Among all the formulations, F3 possess satisfactory swelling index, and *in vitro* drug release studies were extended period of time so F3 was considered to be the best formulations. So, Miconazole nitrate used for the treatment of pain as transferosomal gel can produce fast absorption. The

study conducted so far reveals promising result suggesting scope for pharmacodynamic and pharmacokinetics evaluation.

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