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Research Article

Effects of Various Emulsifying Agent and Permeability Enhancer on Percutaneous Absorption of Novel Microemulsion-Based Cream

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Abstract

Terbinafine hydrochloride is an antifungal drug used in the treatment of fungal infections. The oral use of terbinafine hydrochloride is not recommended as it has many potential side effects and undergoes hepatic first pass metabolism. Topical route of application has a great potential as an effective and safe way to administer drug for its antifungal in effect. The concentration of surfactant and permeation enhancer significantly affects the critical parameters of cream formulation like flux, cumulative amount released at 12 hours and enhancement ratio. In vitro permeation study across rat epidermal membrane showed that menthol enhanced the transdermal absorption of drug from cream formulation. The topical cream formulation developed in this study holds the promise for the further in vivo studies. The aim of the present work under investigation is to check the effects of emulsifying agents (Cremophor RH40, Tween 60) and permeation enhancers (l-Menthol) on cream. Developing a formulation that is safe and can deliver the drug locally in an effective concentration for its effect. The development of topical antifungal drug delivery systems designed to have localized effects appears to be very advisable and beneficial over conventional routes of provides the drug administration. However, due to the relative impermeability of the stratum corneum, which principal resistance to percutaneous absorption, extensive studies are generally necessary in order to optimize both the release of the drug from the topical vehicle and skin permeation further, A topical formulation must be both physically and chemically stable, this require numerous excipients. Aesthetically pleasing, in addition to being properties, hence they play emulsifying agents and permeation enhancers have major influence on these important role.

Keywords: Emulsifying agents, Permeation enhancers, Stratum corneum, Antifungal, Topical cream

INTRODUCTION

The development of topical drug delivery systems designed to have systemic effects appears to be beneficial for a large number of drugs on account of the several advantages over conventional routes of drug administration in order to optimize both the release of the drug from the topical vehicle and skin permeation[1] . The topical antifungal agents have varying mechanisms of action and different spectrums of activity and have few adverse reactions or drug interactions. Creams are widely used in the cosmetic and pharmaceutical fields for the topical administration of hydrophilic and lipophilic active ingredients. There exist different types of emulsions, e.g. water-in-oil, oil-in-water, water-in-oil-in-water and oil-in-water in-oil. Furthermore, emulsions are thermodynamically unstable and necessitate an emulsifier for the formation and stabilization. Both, the type of emulsion and emulsifier could affect dermal and transdermal delivery. Creams are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base. This term traditionally has been applied to semisolids that possess a relatively soft, spreadable consistency formulated as either water-in-oil or oil in water emulsions. However, more recently the term has been restricted to products consisting of oil in water emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable[2, 3]. Microemulsions are clear, stable, isotropic mixtures of oil, water, and surfactant, frequently in combination with a cosurfactant[4-6]. Microemulsions have several advantages such as enhanced drug solubility, good thermodynamic stability and higher transdermal permeability over conventional formulations[7,8]. Many studies reported the use of microemulsions as topical drug delivery vehicles showed their ability to improve transdermal and dermal delivery properties[8-10]. Microemulsions have several permeation enhancement mechanisms such as increase in concentration gradient and thermodynamic activity toward the skin[11]. The aim of present studies the effects of various emulsifying agent and permeability enhancer on percutaneous absorption of novel microemulsion-based cream.

MATERIALS AND METHODS

Materials

Terbinafine hydrochloride was obtained as a gift sample from Macleods Pharmaceuticals, Mumbai. Cremophor RH40, Tween60, was purchased from Himedia Laboratory, Mumbai. IPM, Cetyl alcohol, l-Menthol, Benzyl alcohol and carbopol-940 purchased from CDH chemical Pvt. Ltd. New Delhi. 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.

Methods

The purpose of preformulation study was to establish physicochemical parameters of drug, physical characteristics & compatibility with common excipients. Various parameters like melting point, solubility and drug excipients compatibility studies etc. were carried out.

Drug-excipient compatibility study

DSC spectra study

Differential Scanning Calorimetry (DSC) Analysis is performed for drug excipients compatibility study. Differential scanning Calorimetry (DSC) was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter. The instrument comprised of calorimeter (DSC60), flow controller (FCL60), thermal analyzer (TA60) and operating software (TA 60). The samples (drug alone or mixture of drug and excipients) were heated in sealed aluminum pans at a scanning rate of 10°C/min from 40 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the drug and drug-polymer mixture. The physical mixtures of drug with different excipients for compatibility studies were prepared by triturating drug and additives in a dried mortar for 5 min.

FTIR spectra study

FTIR spectra were obtained on a Shimadzu 8400S FTIR spectrometer (Shimadzu, Japan).Samples were prepared in KBr disks. The scanning range was 400 to 4000 cm−1 and theresolutionwas1 cm−1.

Calibration curve of drug in methanol at 223nm

Weighed quantity of drug (10 mg) was dissolved in 20 ml methanol and volume was made up to 100 ml in volumetric flask using methanol (100µg/ml). From this stock solution, 1ml solution was withdrawn and diluted upto10 ml in volumetric flask (10µg/ml). Same way solutions having different concentrations of 5, 10, 15, 20, 25, 30µg/ml were prepared. Absorbance of each solution was measured at 223 nm using Shimadzu UV-1800 UV/Visible double beam spectrophotometer and Methanol as a reference standard.

Preparation of cream

Preparation of cream was done by emulsifying procedure in which at the same temperature of lipophilic phase and aqueous phase was thoroughly mixed. In the separate vessel lipophilic phase and aqueous phase was prepared. For the lipophilic phase, lipophilic ingredients, cetyl alcohol, IPM, cremophor RH40 was melted in a porcelain dish at 65-75°C. For the aqueous phase, hydrophilic ingredient, water, tween 60 and drug was mixed and heat at temperature of65-70°C.After melting the lipophilic ingredient, heating was stopped, aqueous phase added slowly and mixed properly. After completion of addition of all ingredients the homogeneous mixing for 10-15 minute with effective cooling was done to achieve better cream formulation.

Full factorial design

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man hours and raw materials. Designing drug delivery formulations with the minimum number of trials is very crucial for pharmaceutical scientists[12]. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions[13]. The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Yi) is measured for each trial.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_{12} + b_{22}X_{22}$$

Table 1: Full factorial design layout

Batch No	X_1(concentration of Cremophor RH40)	X_2(concentration of Tween60)
F1	-1(2.5%)	-1(1%)
F2	-1(2.5%)	0(2.5%)
F3	-1(2.5%)	1(5%)
F4	0(5%)	-1(1%)
F5	0(5%)	0(2.5%)
F6	0(5%)	1(5%)
F7	1(7.5%)	-1(1%)
F8	1(7.5%)	0(2.5%)
F9	1(7.5%)	1(5%)

Table 2: Coded values for % concentration of cremophor RH40 (X_1) and tween 60 (X_2)

Coded value	% Concentration of Cremophor RH 40 (X_1)	% Concentration of Tween 60 (X_2)
-1	2.5	1
0	5	2.5
1	7.5	5

Table 3: Formulations using 3^2 full factorial design (%w/w)

Batch no	F1	F2	F3	F4	F5	F6	F7	F8	F9
Terbinafine	1	1	1	1	1	1	1	1	1
Carbopol 940	1	1	1	1	1	1	1	1	1
Cremophor RH40	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5
Tween60	1	2.5	5	1	2.5	5	1	2.5	5
IPM	10	10	10	10	10	10	10	10	10
Cetyl alcohol	5	5	5	5	5	5	5	5	5
Benzyl alcohol	1	1	1	1	1	1	1	1	1
Distill Water q.s To make	100	100	100	100	100	100	100	100	100

*All the Quantity is in percentage

Effect of permeation enhancer

After achieving better cream formulation in preliminary trials by optimized concentration of surfactant, further achievement of better cream formulation, optimization of the penetration enhancer also very important.The addition of permeation-enhancing compounds to topical delivery systems may improve the penetration of drugs by modifying the thermodynamic activity of penetrants (e.g.,changes in partitioning tendencies)or by altering the skin barrier properties (e.g., changes in fluidity of extracellular lipids). Menthol, terpenes etc. may cause a reversible disruption of the lipid domain and promote the formation of new polar channels. The presence of penetration enhancers may also change the thermodynamic activity of the drug in the vehicle and consequently alter its permeability. L-Menthol is a terpenes compound containing alcohols that has been widely used as skin penetration enhancers for a variety of compounds. Menthol was selected for our studies because it is also a refrigerant agent that induces a strong cooling sensation when applied to the skin and numbs the sensation of pain, for this reason, it may provide an advantage for antifungal topical formulations. Permeation enhancement of menthol could involve its distribution into the intercellular space of stratum corneum and the possible reversible disruption of the intercellular lipid domain. This would increase drug diffusivity. L-Menthol was taken as permeation enhancer in concentration of 1, 5, 10% in the optimized surfactant formulation to achieve best permeation from the cream formulation. The formulations of the optimization of permeation enhancer concentration batches (F10-F12) are shown in Table 4.

Table 4: The formulations for the optimization of permeation enhancer concentration batches (F10-F12)(%w/w)

Batch no	F10	F11	F12
Drug	1	1	1
Carbopol940	1	1	1
CremophorRH40	7.5	7.5	7.5
Tween60	2.5	2.5	2.5
IPM	10	10	10
Cetyl alcohol	5	5	5
Benzyl alcohol	1	1	1
Menthol	1	5	10
Distilled water q.s to make	100	100	100

*All the Quantity is in percentage

Independent variables

X_1–ConcentrationofCremophoreRH40X_2 – Concentration ofTween 60

Dependent variables

Y_1 –The flux (j)

Y_2 - Cumulative amount released at 12 hours (Q_{12}), Y_3 - Enhancement ratio (ER)

Evaluation of cream

pH measurements

The pH was measured in each cream formulation, using a pH meter (Systronic, 361-micro pH meter), which was calibrated before each use with buffered solutions at pH 4and pH 7. About 20gm of the cream was subjected to pH measurement within 24 hours of manufacture. An average pH reading of three readings was recorded.

Viscosity measurements

A Brookfield Rotational Digital Viscometer DV II RVTDV-II was used to measure the viscosity (in cps) of the cream formulations. The spindle was rotated at 10 rpm. Samples of the creams were allowed to settle over 30 minutes at the assay temperature (25±1^{o}C) before the measurements were taken.

Spreadability measurements

For the determination of spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1000 gm weight for 5mins.Weight(50gm)was added to the pan. The time required separating the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of spreadability(s). S=ml/t

Determination of extrudability

It is a useful empirical test to the measure the forces to extrude the material from a tube. Since the packing of creams have gained a considerable importance in delivery of desired quantity of cream from jar of extrusion of cream collapsible tube, therefore measurement of extrudability becomes an important criterion for creams. The cream formulation was filled in standard caped collapsible lami-tube and sealed. The tube was weighted recorded. The tube was placed between two glass slides and was clamped. A 500gm weight was placed over the glass slide and then glass slides and was clamped. A 500gm weight was placed over the glass slide and then cap was opened. The amount of cream extruded were collected

and weighted. The % of cream extruded was calculated.

Drug content

The drug content of the prepared cream was carried out by dissolving accurately weighed quantity (0.5g) of cream equivalent to10mg of drug was dissolved in10ml of methanol, the volume was made up to 100 ml and 5 ml of the above solution was diluted further to 25 ml with methanol. After suitable dilution absorbance of the solution was recorded by using Shimadzu UV/ visible spectrophotometer at 223 nm.

***Invitro* skin permeation studies**

The release rates from different cream formulations were measured through rat skin. The dorsal skin of nude rat was mounted on the Franz diffusion cells with a diffusional area of 1.86 cm^2 and a receiver compartment volume of 20 ml. The receptor compartment contained pH7.4 phosphate buffer saline and methanol in ratio of 70:30. To allow the establishment of the sink condition and to sustain permeant solubilization, receptor phase was stirred and thermo stated at 37±0.5°C during the experiments. 500 mg of each cream formulation was placed with 2 mm thick layer on the diffusion barrier in the donor compartment. At appropriate time intervals samples from receptor compartment were withdrawn and replaced with fresh solution. This dilution of the receiver content was taken into account when evaluating the penetration data. The samples were analyzed spectrophotometrically (UV spectrophotometer, Shimadzu 1800, Japan) at a wavelength of 223 nm and the concentration of drug in each sample was determined from a previously calculated, standard curve. The total amount of drug penetrating through the unit membrane surface and diffusing into the receptor medium was calculated and plotted as a function of time.

Drug release kinetics study

The results of in-vitro release profile obtained for all the formulations were plotted in kinetic models as follows,

1. Cumulative of drug released versus time (zero order kinetic model).

2. Log cumulative percent drug remaining to be absorbed versus time (First order model)

3. Cumulative amount of drug release versus square root of time (Higuchi model)

4. Log cumulative drug released versus log time (Korsmeyer-Peppas model) [14, 15].

Stability study

Selected formulation F12 was stored in lamitube (well stoppered) for three months and the stability was monitored up to 2months at accelerated stability conditions (45°Ctemperature and 75±5%RH.). Periodically (initial, 1 and 2 months interval) samples were removed and characterized by pH, viscosity, drug content and drug release.

RESULTS AND DISCUSSIONS

The absorption maxima of terbinafine hydrochloride were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer (Shimadzu UV-1800) using concentration range of 5-30µg/ml terbinafine hydrochloride in methanol. Terbinafine hydrochloride showed a linear relationship with correlation coefficient of 0.999 in the concentration range of 5-30µg/ml in methanol. All the data of preformulation study were found similar as given in standard monograph which confirmed that the drug was authenticated and pure in form and it could be used for formulation development of terbinafine hydrochloride cream. DSC thermogram and FTIR spectra of drug was given in Figure 1& 2. The pH of the cream formulations was in the range of 5.22±0.1 to 5.89± 0.2 (Table 5) which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulations. The data on viscosity study indicated that with constant concentration of the Cremophor RH40, increase in concentration of the Tween 60 viscosity of formulation was also increased and with constant concentration of the Tween 60 increase in concentration of the Cremophor RH40 viscosity of formulation was also increased. So with both the emulsifying agents viscosity was found to be increased with increase in concentration (Table 5). Spreadability of cream was evaluated to test the ease of applicability of creams on skin. The spreadability of the formulation was between 11.6±0.85 to 13.80±0.30 gm.cm/sec which showed good spreadability (Table 5) and it was found to be comparable with the spreadability of marketed product. Extrudability of cream was evaluated to measure the forces to extrude the material from a tube. Since the packing of creams have gained a considerable importance in delivery of desired quantity of cream from jar of extrusion of cream collapsible tube, therefore measurement of extrudability becomes an important criterion for creams. The extrudability of the formulation was between 91.61±0.80to94.27±0.32percent (Table 5) which was found to be comparable with the marketed product. The drug content of the cream preparation was found to be uniform among various formulations prepared and was found to range from 98.23±0.30% to 100.6±0.34 %. The drug content determination also showed that the all the formulations pass the acceptable drug content limit (Table 5). From the result shown in Table 6, the in vitro drug release of batch F1, F2, F3,F4 & F5were best explain by zero order kinetics as a plot showed highest linearity (R^2).The invitro drug release of batch F6, F7, F8 & F9 were best explained by korsmeyer-peppas model. In case of F1 to F4, drug was released by Non-Fickian model (because n > 0.5) as shown in Table 6. Among all batches from F1 to F9, F4 and F6 showed highest linearity (R^2 =0.9990). The cumulative amount of drug released from creams was determined and showed in Table 7.Each data point represents the mean of 6 determinations. The amount of drug was constantinall different cream formulation. Among all cream formulations, formulations containing 2.5% Cremophor RH40 and 1% Tween 80 showed the lowest release (31.05±0.15) of drug in 12h and formulations containing 7.5% Cremophor RH40 and 2.5% Tween 60 showed the highest release (47.10±0.24) of drug in 12 h. Hence, this concentration was selected for preparing cream formulations to study the effect of menthol as permeation enhancer. The effect of surfactants on the permeability of drug across the rat skin from cream formulations was investigated. The release profile showed the higher release rate was observed in the F8 batch. Permeation parameters for drug from the cream formulations are shown in Table 7. A marked effect of surfactants, concentration of cremophor RH40 and concentration of Tween 60 on drug permeation was observed when it was incorporated cream formulations. The cumulative amount permeated at 12 hours (Q_{12}) of drug was 155.80±0.89µg from cream formulation F8. The corresponding flux (J) and enhancement ratio (ER) drug was 3.914±0.20µg $cm^{-2}hr^{-1}$ and1.93±0.45 respectively for the cream formulation F8. The statistical analysis of the factorial design batches was performed by multiple linear regression analysis carried out in Designexpert8.0.7software.The values for J, ER and Q_{12} for all 9 batches (F1toF9) are showed in Table 7. The data clearly indicated that the values of J, ER and Q_{12} were strongly dependent on the independent variables. The fitted equations relating the J, ER andQ_{12} to the transformed factor are shown in following Equations 1, 2and 3.

$$J=2.98 +0.79 (X_1) +0.39 (X_2) +1.80(X_{11})+0.057(X_{22})+0.17(X_1)(X_2) \quad (1)$$

$$Q_{12}=97.95 +32.58(X_1) +19.58(X_2) +4.13(X_{11}) + 0.88(X_{22})+13.97(X_1)(X_2) \quad (2)$$

$$ER= 1.47 +0.39(X_1) +0.19(X_2) +2.89 (X_{11}) +0.032 (X_{22}) +0.086 (X_1)(X_2) \quad (3)$$

Regression analysis of 3^2full factorial design was employed to study the effect of independent variables, i.e. concentration of cremophor RH40 (X_1) and concentration of tween 60 (X_2) on dependent variables like flux (J), %drug release at 12 hrs (Q_{12}) and enhancement ratio (ER). The results as summarized in below Figure 3 to 8. The results clearly indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (F1toF9). The formulation batch F8 was selected for optimization as it showed the good drug release as compared to other formulation batches. Incorporation of permeation enhancer was done in F8 batch and three more formulation batches were taken namely F10, F11, and F12. The varying quantities of menthol as permeation enhancer taken in 3 different formulation F10, F11, F12 was 1%, 5%, 10%w/w respectively and all the three batches were evaluated for the parameters namely flux, drug release at 12 hrs, and enhancement ratio. The corresponding flux were found to be 3.914±0.20, 5.161±0.20, 6.062±0.16 and7.456±0.10µg $cm^{-2}hr^{-1}$ for cream formulations containing 0, 1, 5, and 10 %w/w of menthol respectively. The Q_{12} values were ranging from 155.80±0.89, 253.24±0.12, 305.12±0.40and373.63±0.60µg.$cm^{-2}hr^{-1}$ and the % drug release was found to be 47.10±0.24,58.32±0.30,66.10±0.52,80.21±0.12% for cream formulation containing 0,1, 5 and 10%w/w of in formulation batches F10, F11, F12 respectively. Amongst all three formulation batches, the formulation batch F12 with menthol 10%w/w showed best results. It showed highest drug release 80.21±0.12%and it is comparable with the drug release of marketed product 82.60±0.70%. As menthol concentration was increased from 0 to 10% w/w, the permeability of drug was also increased as indicated by an increase in ER (Table 8). Short-term stability study of optimized batch was carried out for 2 months at accelerated stability conditions. All the data are mentioned in Table 9. Stability study revealed that no any major changes taken place throughout the stability study for 2 months so we can say that formulation F12 has good stability.

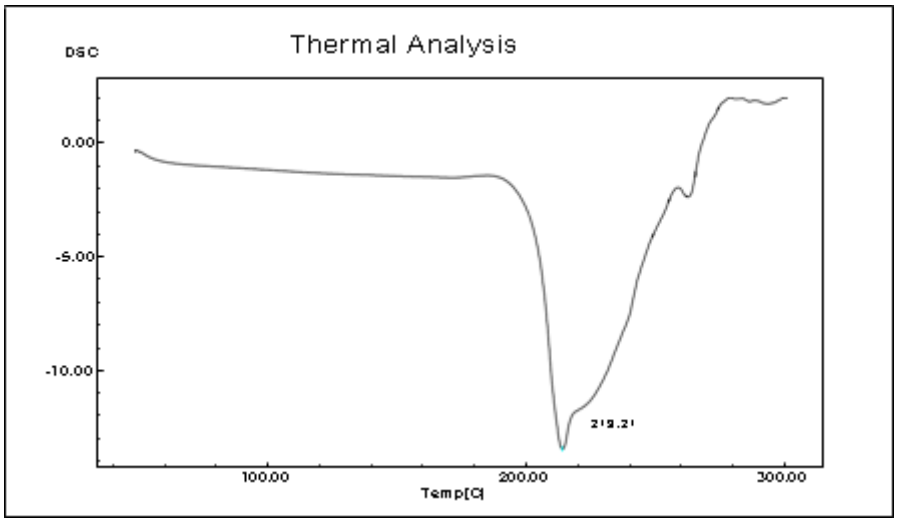

Figure 1: DSC thermogram of drug

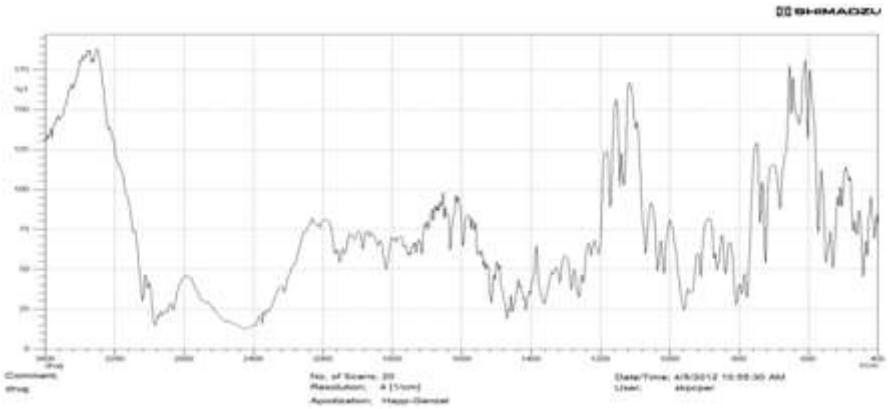

Figure 2: FTIR spectra of drug

Table 5: Physical characterization of cream formulation F1toF9

Batch No	pH	Viscosity (cps×10³)	Spreadability (gm.cm/sec)	Extrudability (%)	Drug content (%)
F1	5.22±0.1	683±4.24	13.23±1.13	92.33±0.45	99.05±0.20
F2	5.40±0.2	692±5.30	12.6±0.63	93.20±1.23	98.4±0.45
F3	5.48±0.3	714±3.45	13.64±1.02	93.31±0.89	99.6±0.24
F4	5.37±0.1	710±5.56	11.74±1.64	94.27±0.32	99.34±0.67
F5	5.41±0.2	725±7.30	12.59±0.80	91.61±0.80	98.23±0.30
F6	5.67±0.4	697±2.33	13.64±1.03	93.56±0.72	99.07±0.80
F7	5.89±0.2	707±1.77	11.6±0.85	93.31±1.12	100.6±0.34
F8	5.32±0.1	695±8.90	13.80±0.30	92.57±0.39	98.35±0.50
F9	5.45±0.2	715±3.40	13.50±0.45	91.90±1.10	100.2±0.98
Market formulation	5.35±0.1	687±8.90	12.85±0.30	93.68±0.39	99.95±0.10

Table 6: Result of model fitting (R^2)

Formulation	Zero order kinetics	First order kinetics	Higuchi model	Korsmeyer–Peppas model	n (release exponent)
F1	0.995	0.993	0.880	0.966	0.460
F2	0.995	0.991	0.883	0.977	0.471
F3	0.997	0.994	0.881	0.973	0.487
F4	0.999	0.996	0.897	0.977	0.498
F5	0.996	0.990	0.879	0.985	0.511
F6	0.984	0.972	0.878	0.999	0.516
F7	0.989	0.978	0.882	0.997	0.516
F8	0.993	0.983	0.882	0.995	0.534
F9	0.996	0.989	0.884	0.997	0.528

Table7: Permeation parameters of cream formulation F1to F9

Batch No	J(μghr^{-1}cm^{-2})	ER	Q_{12}(μg)	%Released
F1	2.024±0.16	1	77.46±1.28	31.05±0.15
F2	2.232±0.18	1.10±0.23	88.46±1.80	33.07±0.07
F3	2.435±0.46	1.20±0.12	89.36±0.70	34.44±0.22
F4	2.653±0.62	1.31±0.20	97.23±0.62	36.06±0.62
F5	2.953±0.40	1.45±0.27	108.33±0.80	38.52±0.40
F6	3.448±0.08	1.70±0.02	135.06±0.74	43.44±0.39
F7	3.281±0.04	1.62±0.32	116.33±0.64	41.87±0.16
F8	3.914±0.20	1.93±0.45	155.80±0.89	47.10±0.24
F9	3.617±0.02	1.78±0.09	144.20±1.87	44.02±0.60

Table 8: Permeation parameters of optimized cream formulation

Batch No	J(μghr^{-1}cm^{-2})	ER	Q_{12}(μg)	%Drug released
F8	3.914±0.20	1	155.80±0.89	47.10±0.24
F10	5.161±0.20	1.31±0.12	253.24±0.12	58.32±0.30
F11	6.062±0.16	1.54±0.09	305.12±0.40	66.10±0.52
F12	7.456±0.10	1.90±0.05	373.63±0.60	80.21±0.12
Marketed Formulation	7.741±0.55	1.97±0.21	382.59±0.32	82.60±0.70

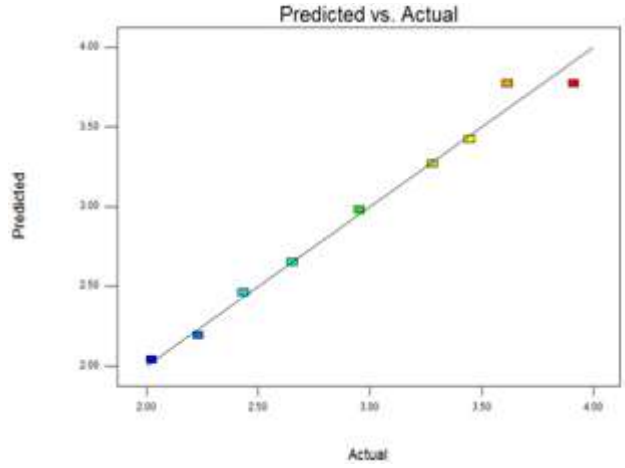

Figure 3: Predicted Vs actual flux

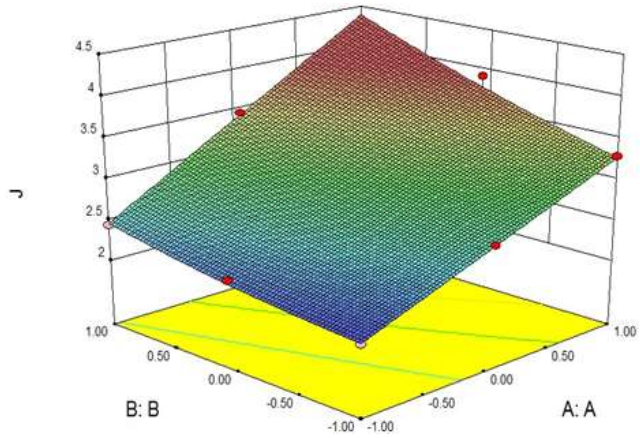

Figure 4: 3D surface plot showing effect of X_1andX_2onflux

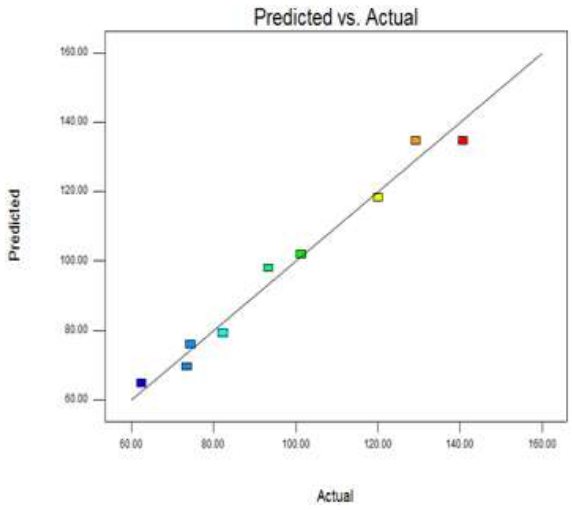

Figure 5: Actual Vs predicted Q_{12}

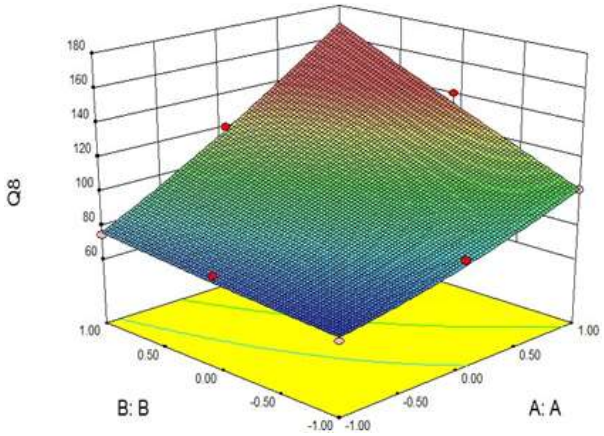

Figure 6: 3D surface plot showing effect of X_1 and X_2 on drug release at 12hrs.

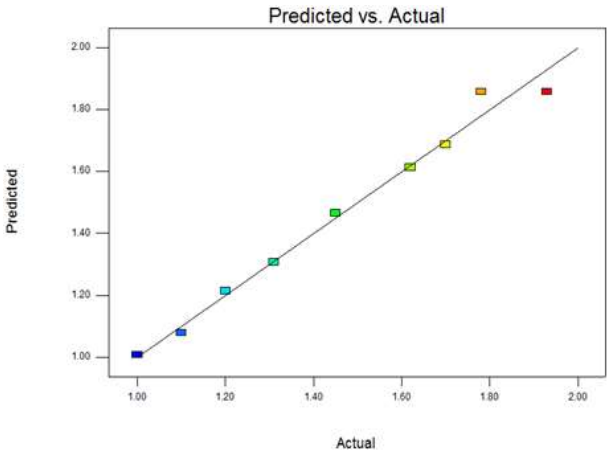

Figure7: Actual Vs predicted ER

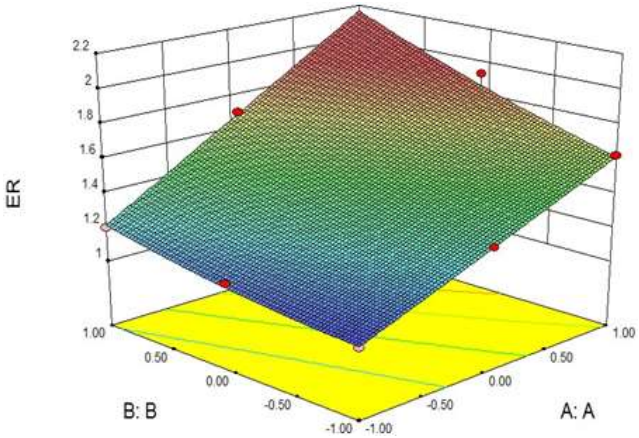

Figure 8: 3D surface plot showing effect of X_1andX_2 on enhancement ratio

Table 9: Evaluation of accelerated stability study of optimized batch

Evaluation parameters	Time period for sampling		
	Initial	1month	2month
pH	5.40±0.1	5.39±0.1	5.37±0.2
Viscosity(cps*10^3)	698.23±0.12	697.12±0.23	695.78±0.62
Drug content (%)	99.34±0.21	99.01±0.12	99.00±0.55
% Drug released	80.21±0.12	79.95±0.15	78.20±0.24

CONCLUSION

Topical route of application has a great potential as an effective and safe way to administer drug for its antifungal in effect. The concentration of surfactant and permeation enhancer significantly affects the critical parameters of cream formulation like flux, cumulative amount released at 12 hours and enhancement ratio. In vitro permeation study across rat epidermal membrane showed that menthol enhanced the transdermal absorption of drug from cream formulation. The topical cream formulation developed in this study holds the promise for the further in vivo studies and can be extrapolated for further development in treatment of fungal disease.

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