

Formulation and Evaluation of Transungual Drug Delivery of Fluconazole Using Permeation Enhancers Screened by Hydration of Nail Plate

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Abstract

The objective of the work was to formulate nail lacquer containing fluconazole an antifungal drug for the treatment of onychomycosis. Onychomycosis, a common fungal nail infection affects the people. Topical and ungual therapy is limited because of the poor permeation of the drug through nail plate. Film base was prepared using varying concentration of cellulose acetate and ethyl cellulose as polymers. The permeation enhancers were screened by nail plate hydration. The formulation was optimized using Box-Behnken design. Various physicochemical parameters like nonvolatile content, drying rate, gloss, smoothness to flow, % CDR for nail lacquer was analyzed out. All the above parameters showed satisfactory results and were within the prescribed limits. Optimum formula suggested by Design Expert software was formulated. The optimum batch shows % CDR was satisfactory and the release kinetics was of zero order. Zone of inhibition and drying time was in range with the standard. The accelerated stability studies showed no significant difference in the evaluation parameters. This proved that the formulated nail lacquer was stable. Antifungal nail lacquers with suitable permeation enhancers are far better for the treatment of onychomycosis than cream, gel and solutions. The high permeation rate helps to reduce the treatment period.

Keywords: Onychomycosis, fluconazole, nail lacquer, transungual drug delivery, permeation enhancers, Box-Behnken design

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INTRODUCTION

Topical treatment of skin and nail diseases is desirable in terms of patient acceptability and reduction of side effects associated with systemic drug delivery. This is particularly the case for nail diseases as they are frequently difficult to cure and also require long periods of treatment [1]. The nail plate is a highly keratinized tissue, which is characterized by low permeability to diffusing substance. The nail diseases are widely spread in the population, particularly among elderly and immune-compromised patients. Although the architecture and composition of the nail plate severely limits penetration of drugs and in addition to that, only a fraction of topical drug penetrates across the nail; oral therapies are accompanied by systemic side effects and the drug interactions. For the successful treatment of nail disease, the applied active drug must permeate through the dense keratinized nail plate and reach deeper layers: the nail bed and the nail matrix [2].

Horny structure of nail plate is responsible for penetration of drug across it. As it is hard enough, the penetration becomes difficult, only a fraction of topical drug penetrates across it. Hence the effective therapeutic concentration is not achieved. The nail plate may appear abnormal, as a result, variety of diseases occur. These diseases can be cured by achieving desired therapeutic concentration of drug by nail drug delivery system [3].

The success of local topical therapy for onychomycosis depends on the achievement of effective chemical concentrations into/through the human nail plate; therefore, a suitable antifungal drug must be coupled with an appropriate delivery method. The method should maximize the effect of the active principle by aiding its diffusion into the nail bed to levels exceeding the minimum inhibitory concentration (MIC) against local infection by dermatophytes. Thus, a suitable carrier may be needed to enhance drug

penetration through the nail barrier [4]. Dermatologists and podiatrists have long used mechanical methods of enhancing nail penetration, including nail abrasion and nail avulsion, but these methods have varying results in addition to being invasive and potentially painful. Thus, current research focuses on less invasive chemical and physical modes of nail penetration enhancement.

MATERIALS AND METHODS

Materials

The following materials were used (Grade-LR): Fluconazole – API, Cellulose Acetate, Ethyl Cellulose (Yarrowchem Products, Mumbai), Triethyl Citrate (S. Zhaveri Pharmakem Pvt. Ltd., Mumbai), Hydroxypropyl Beta Cyclodextrin (Gangwal Chemicals Pvt. Ltd., Thane), N-acetyl-l-cysteine (Vision Scientific, Angamaly), 2-Mercapto ethanol (Calgon Scientific Co., Edappally), Isopropyl Alcohol, Acetone (Nice Chemicals Pvt. Ltd., Cochin.), Ethanol, Methanol (Chemco Chemicals Pvt. Ltd., New Delhi).

Methods

Preformulation Studies [5, 6]

Determination of Melting Point

Melting point of fluconazole, ethyl cellulose and cellulose acetate were determined by capillary method, using Thiele's apparatus.

FT-IR Spectroscopy

FT-IR spectroscopy was carried out to check the compatibility between drug and polymer. The compatibility between fluconazole, ethyl cellulose and cellulose acetate was carried out in the ratio of 1:4:4.

Solubility

Solubility of fluconazole, ethyl cellulose, and cellulose acetate was tested in various solvents such as distilled water, methanol, ethanol, propylene glycol and acetone.

Formulation Studies of Film [7, 8]

Preparation of Film

The film base was prepared using cellulose acetate and ethyl cellulose as film forming polymers, triethyl citrate as plasticizer, isopropyl alcohol and acetone as solvents. The formulation trials were done as per the formula given in Table 2. The film was prepared by

adding cellulose acetate in acetone and ethyl cellulose in isopropyl alcohol under continuous stirring. Both the solutions were mixed together and triethyl citrate was added to it under stirring till a clear solution was formed. The measured amount of distilled water was added to the resulting solution and mixed well and stored in air tight container.

Film Thickness [9–13]

The thickness of the film was measured by using screw gauge with a least count of 0.01 mm at different spots at the films. The thickness was measured at five different spots of the film and average was taken.

Folding Endurance [9–13]

Folding endurance of the films was determined by repeatedly folding a small strip of the film (approximately 2×2 cm) at the same place till it broke. The number of times film could be folded at the same place, without breaking gives the value of folding endurance.

Water Resistance [9–13]

This is the measure of the resistance towards water permeability of the film. This was done by applying a continuous film on a surface and immersing it in water. The weight before and after immersion, was noted.

Selection of Permeation Enhancers by Hydration of Nail Plate [14]

Preparation of Nail Clippings

The nail clippings were collected from healthy human volunteers (male and female, age 15–30). The nail clippings were washed three times with 70% v/v ethanol followed by rinsing with distilled water. They were dried overnight in an open petridish at room temperature. The dried nail clippings were either used immediately or stored at controlled temperature (2–8°C) in aluminum capped vials. The nail clippings were cut into pieces of 5×5 mm size and characterized for average thickness and weight.

Screening of Transungual Drug Permeation Enhancer by Hydration Enhancement Factor [14]

Nail clipping was weighed and placed in a glass vial filled with 1 ml permeation enhancer solution (Table 1). In another glass vial, a control was also simultaneously run by placing

a nail clipping in 1 ml distilled water. The glass vials were sealed and incubated at room temperature for 24 h. Nail clippings were then removed from glass vials and wiped with tissue paper to remove any water/solution residue on their surface. These nail clippings were weighed and weight gain was calculated and reported as hydration enhancement factor for screening the selected transungual permeation enhancers.

Optimization of Fluconazole Nail Lacquer [15]

Response surface methodology using Box-Behnken was chosen for the optimization of nail lacquer formulation because it allows the determination of influence of the factors with a minimum number of experiments. The independent factors were hydroxyl propyl beta cyclodextrin concentration (X1), N-acetyl-l-cysteine (X2) and 2-mercapto ethanol (X3). The response variables were: cumulative drug release (%) (Y1), and drying time (sec) (Y2). 17 formulations were prepared according to Box-Behnken design.

Evaluation of Nail Lacquer [8, 16]

Drug Entrapment

Drug content of nail lacquer was determined by dissolving accurately 1 ml of nail lacquer in methanol. After suitable dilution, absorbance was recorded by using UV-visible spectrophotometer at 261 nm.

Nonvolatile Content

1 gm of sample was taken in a glass petridish of about 8 cm in diameter. Samples were spread evenly. The dish was placed in the oven at 105°C for 1 h. The petridish was removed, cooled, and weighed. The difference in weight of sample after drying was determined and was recorded as volatile content.

Drying Time

A film of sample was applied on a glass petridish with the help of brush. The time to form a dry film was noted using a stopwatch.

Smoothness of Flow

The sample was poured on a glass slide on an area of 1.5 square inches and spread on a glass plate by making glass slide to rise vertically. Smoothness of flow was determined by

comparing with standard marketed nail lacquer.

Gloss

Gloss of the film was visually seen and was compared with a standard marketed nail lacquer.

Diffusion Studies across Artificial Membrane

Diffusion studies were performed using artificial membrane (cellophane). The membrane was soaked for 1 h in solvent system (phosphate buffer, pH 7.4), and the receptor compartment was filled with solvent. Test vehicle equivalent to 10 mg was applied on the surface of the membrane. The prepared membrane was mounted on the cell carefully to avoid entrapment of air bubbles under the membrane. The whole assembly was maintained at 37°C, and the speed of stirring was kept constant (600 rpm) for 10 h. The 5 ml aliquot of drug sample was withdrawn at 1, 2, 3, 4, 5, 6, 8 and 10th h and was replaced by fresh solvent. The drug analysis was done using double-beam UV spectrophotometer.

Development of the Optimum Batch

Based on the statistical evaluations the software suggested one optimum batch.

Evaluation of the Optimized Batch of Nail Lacquer

Drying Time [8, 16]

A film of sample was applied on a glass petridish with the help of brush. The time to form a dry to touch film was noted using a stopwatch.

In vitro Transungual Permeation Studies [8, 16]

Hooves from freshly slaughtered cattle, free of adhering connective and cartilaginous tissue, were soaked in distilled water for 24 h. membranes of about 1 mm thickness were then cut from the distal part of hooves. *In vitro* permeation studies were carried out by using franz diffusion cell, the hoof membrane was placed carefully on the cell, and the surface area available for permeation was 1.4 cm². Then the test vehicle equivalent to 10 mg was applied evenly on the surface of the nail membrane. The receptor compartment was filled with solvent (phosphate buffer, pH 7.4),

and the whole assembly was maintained at 37°C with constant stirring for 30 h. The 5 ml aliquot of drug sample was taken after a time interval of 0, 2, 4, 6, 8, 10, 14, 18, 22, 26, 30 h and was replaced by fresh solvent. The drug analysis was done by using double-beam UV spectrophotometer.

Determination of Zone of Inhibition [17]

Candida albicans were employed for testing antifungal activity using the cup plate method. The culture was maintained on sabouraud's agar slants. 20 ml of melted sabouraud's agar medium was inoculated with 72 h old 0.2 ml suspension of *Candida albicans* in the petridish and allowed to set by keeping undisturbed for 15 min. The cups (10 mm diameter) were punched in the petridish and filled with 0.05 ml of a solution of the sample dissolved in DMSO and in another plate, pure drug solution was placed carefully. The plates were kept for diffusion at $\pm 40^\circ\text{C}$ for 1 h, and incubated at 30°C for 48 h. After the completion of incubation period, the zone of inhibition in millimeter was measured.

Kinetics of *In Vitro* Drug Release [18]

To study the release kinetics of *in-vitro* drug release, data obtained from *in-vitro* release study were plotted in various kinetic models:

Zero order as % drug released vs. time, First order as $\log\%$ drug retained vs. time, Higuchi as % drug released vs. $\sqrt{\text{time}}$, Korsmeyer-Peppas as $\log\%$ drug released vs. $\log \text{time}$ and Hixson-Crowell as $(\% \text{ drug retained})^{1/3}$ vs. time. By comparing the r-values obtained, the best-fit model was selected.

Stability Studies [19]

Stability studies were carried at 40°C and 75% RH, in lab top stability testing equipment. The sample was evaluated for nonvolatile content, drying time, gloss, and smoothness of flow, water resistance, drug content and diffusion across artificial membrane.

RESULTS AND DISCUSSION

Preformulation Studies

Melting point of the drug was found to be 139°C, which was in conformity with the reported. Solubility in different solvents were determined and tabulated in Table 1.

The FTIR spectrum of fluconazole with different polymers used in formulation are shown in Figure 1. The major peaks observed in drug spectrum were also observed in spectrum of drug with polymer; therefore it indicates that there was no incompatibility between drug and polymer.

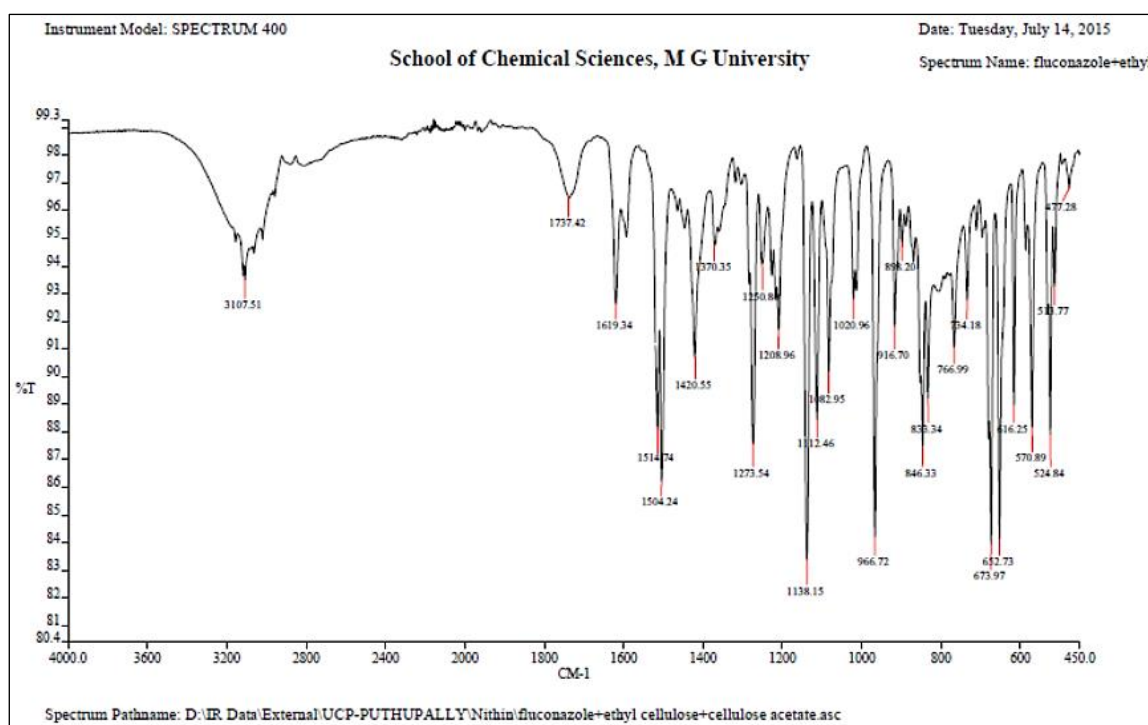


Fig. 1: FT-IR Spectrum of Fluconazole, Cellulose Acetate and Ethyl Cellulose.

Table 1: Solubility Data.

	Water	Ethanol	Methanol	Propylene Glycol	Acetone
Fluconazole	Slightly Soluble	Soluble	Freely soluble	Soluble	Soluble

Formulation Studies of Film

Preparation of Film

The film base was prepared based on Table 2, using cellulose acetate, ethyl cellulose as polymers and acetone and isopropyl alcohol as solvents.

Table 2: Formulation Code for Film.

Ingredients	Concentration (%w/v)				
	FL1	FL2	FL3	FL4	FL5
Cellulose acetate	1	2	3	4	2.5
Ethyl cellulose	4	3	2	1	2.5
Isopropyl alcohol	30	30	30	30	30
Acetone	48.9	48.9	48.9	48.9	48.9
Triethyl citrate	0.1	0.1	0.1	0.1	0.1
Distilled water	15	15	15	15	15

Film Thickness (μm)

Uniform thickness indicates the uniformity of the formulations thereby suitability of the executed procedure. Thickness of all the films was measured by using screw gauge. Results showed that that thickness of all formulations varied from 57 to 60 μm . The observed values were plotted in Graph 1.

Folding Endurance

Folding endurance indicates the flexibility of the polymer film. In order to evaluate the flexibility, the prepared films were subjected to folding endurance studies. The number of folds a film can sustain without break will dictate its folding endurance. The values obtained were above 60 in all of the developed films and are listed in Graph 1. And it was in range of 68 to 94 for all the developed films. The results revealed that the prepared films were having the capacity to withstand the mechanical pressure along with good flexibility. Higher the folding endurance value better will be the flexibility of the films. 2%w/v CA along with 3%w/v of EC (NF2) showed good folding endurance, thereby ensuring good flexibility.

Water Resistance

This is the measure of the resistance towards water permeability of the films. This was done

by applying a continuous film on a surface and immersing it in water. The weight before and after immersion was noted and increase, was calculated. Higher the increase in weight lowers the water resistance. Here, out of all five formulations, FL2 has comparatively low weight and has the better water resistance. The data are mentioned in and Graph 2.

From the above data, it can be concluded that the formulation FL2 which shows an average thickness, high folding endurance and with high resistance towards water is the best suited formulation for the preparation of the nail lacquer.

Selection of Permeation Enhancers by Hydration of Nail Plate

The hydration enhancement factor, HEF_{24} , of nail clippings was determined for each permeation enhancer using Eq. (1).

$$\text{HEF}_{24} = \frac{W_p}{W_c} \quad (1)$$

Where, HEF_{24} = Hydration enhancement factor calculated in 24 h.

W_p = % weight gain of nail clipping exposed to permeation enhancer solution.

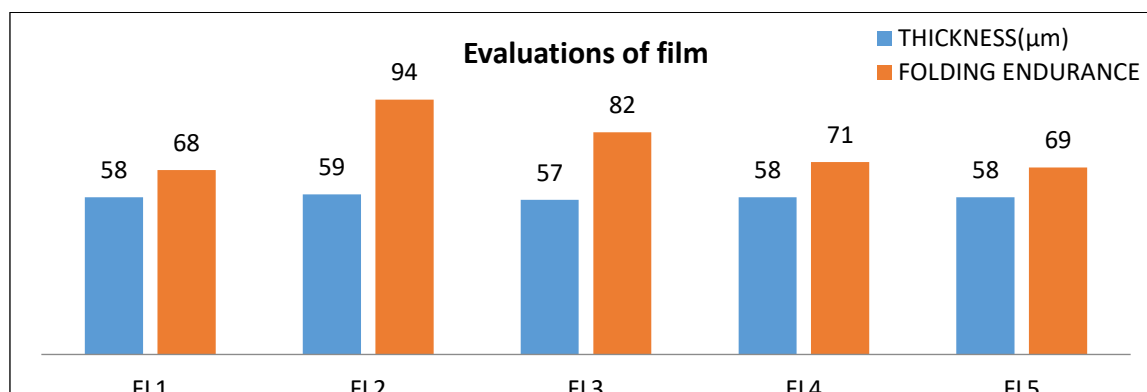
W_c = % weight gain of nail clippings exposed to water (control).

The extent of hydration enhancement of the nail clippings by permeation enhancers was found to be dependent on their individual ability to do any structural or physicochemical changes in the nail clippings. It was hypothesized that the permeation enhancers which affect above properties of nail clippings on a large extent would also affect their water absorption/hydration capacity.

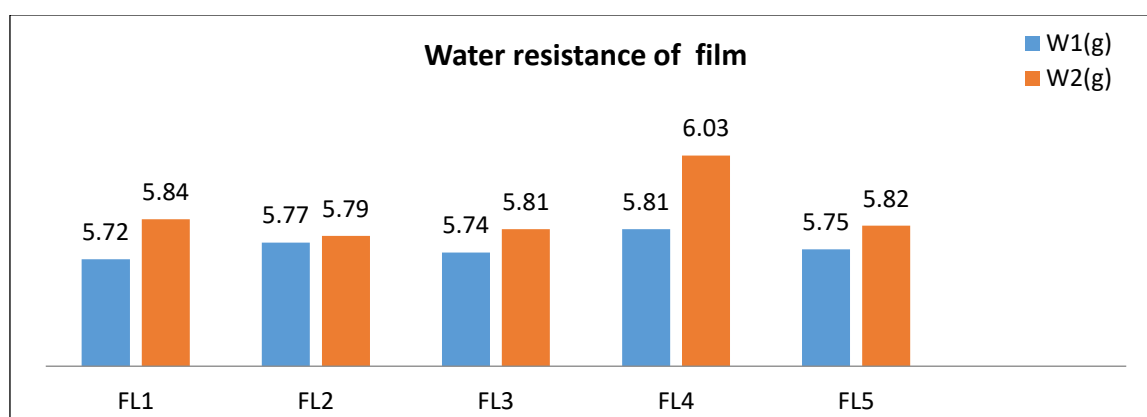
In the study, 19 permeation enhancers were evaluated for their ability to enhance transungual permeation. The hydration enhancement factor, HEF_{24} was calculated using Eq. (1) for the determination of the effect of permeation enhancers on hydration enhancement of nail clippings. Table 3 shows a comparison of HEF_{24} of nail clippings treated by various permeation enhancers. Nail clippings immersed in solutions of N-acetyl-L-

cystine, Hydroxypropyl- β -cyclodextrin, 2-Mercapto ethanol showed maximum HEF_{24} respectively, i.e. 7.415466 ± 0.7324 , 5.685733 ± 0.7324 , and 5.662366 ± 0.5092 , respectively. Hence, N-acetyl-l-cysteine,

Hydroxypropyl- β -cyclodextrin, 2-Mercapto ethanol were proved to be the most effective transungual permeation enhancers as per the proposed hypothesis amongst all the 19 permeation enhancers tested.



Graph 1: Evaluations of Film.



Graph 2: Water Resistance of Film.

W_1 : Weight before Dipping; W_2 : After Dipping.

Table 3: Selection of Permeation Enhancers by HEF_{24} .

S. No.	Permeation Enhancer	Concentration (%w/v)	HEF_{24} (Mean \pm S.D.) (n=3)
1	Papain	5.00	1.415933 ± 0.5931
2	Resorcinol	5.00	1.147263 ± 0.2145
3	Hydroxypropyl- β -cyclodextrin	5.00	5.685733 ± 0.5547
4	Oxalic acid	5.00	1.063553 ± 0.2644
5	Salicylic acid	1.00	1.511196 ± 0.3050
6	Thioglycolic acid	5.00	4.689540 ± 0.2009
7	Glycerin	5.00	1.276606 ± 0.3687
8	PEG-400	5.00	1.354433 ± 0.1747
9	Propylene glycol	5.00	1.335733 ± 0.1834
10	Urea	5.00	1.480266 ± 0.5969
11	Thiourea	2.00	1.381535 ± 0.6364
12	N-acetyl-l-cysteine	1.00	7.415466 ± 0.7324
13	Sodium lauryl sulfate	0.50	1.814533 ± 0.1767
14	Sodium hydroxide	0.08	1.537033 ± 0.3903
15	Tween-20	0.50	0.209733 ± 0.03232
16	Hydrogen peroxide	3.00	0.9238 ± 0.04600
17	Methanol	50.00	1.1489 ± 0.1276
18	2-Mercaptoethanol	1.00	5.662366 ± 0.5092
19	Sodium thiosulfate	5.00	0.9534 ± 0.03732

Optimization of Fluconazole Nail Lacquer

According to Box-Behnken design, 17 formulations of nail lacquer were prepared by varying concentration of Hydroxy propyl β cyclodextrin as X1, N-acetyl-l- as X2 and 2-Mercapto ethanol as X3. The concentrations are shown in Table 4.

Evaluation of Nail Lacquer

Drug Entrapment

Percentage drug content for all the lacquers were in between 90 and 98% which can be seen in Graph 3. Highest % of drug content was found to be 97.458 (F3) and lowest % of drug content was 90.7724 (F5). Drug content more than 90 shows the high amount of drug present in the formulation, without causing any change in the ideal property of nail lacquer.

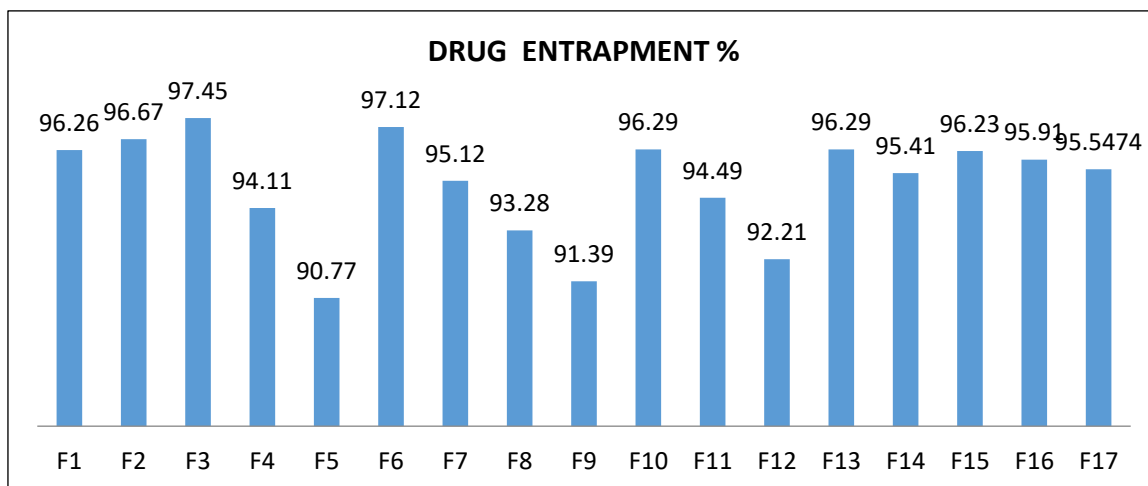
Nonvolatile Content

Desired amount of nonvolatile matter was seen with complete evaporation of volatile matter

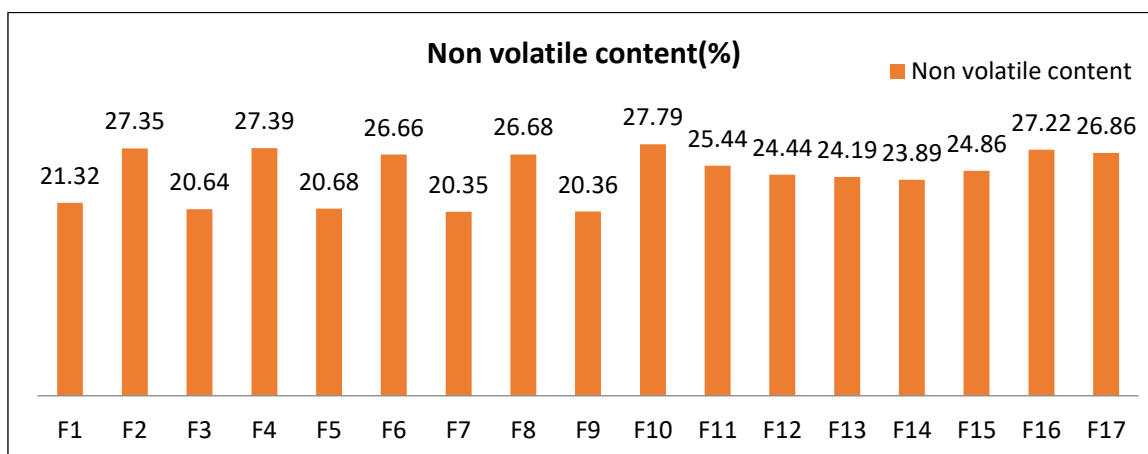
leaving a thin film. It ranges from 20 to 30% and the results are pooled in Graph 4.

Table 4: Formulation Code for Nail Lacquer.

Formulation Code	X1	X2	X3
	HP-B-CD	N-Acy Cys	2Mer Cap Eth
	g	g	ml
F1	5.5	2	2.25
F2	5	2	0.9
F3	6	2	3.6
F4	5.5	3	3.6
F5	6	1	2.25
F6	5.5	2	2.25
F7	6	3	2.25
F8	5	1	2.25
F9	5.5	3	0.9
F10	5.5	2	2.25
F11	5	2	3.6
F12	5.5	1	3.6
F13	6	2	0.9
F14	5	3	2.25
F15	5.5	2	2.25
F16	5.5	1	0.9
F17	5.5	2	2.25



Graph 3: Drug Entrapment.



Graph 4: Nonvolatile Content.

Gloss and Smoothness of Flow

Smoothness of flow and gloss were found to be satisfactory when compared with the marketed cosmetic lacquer.

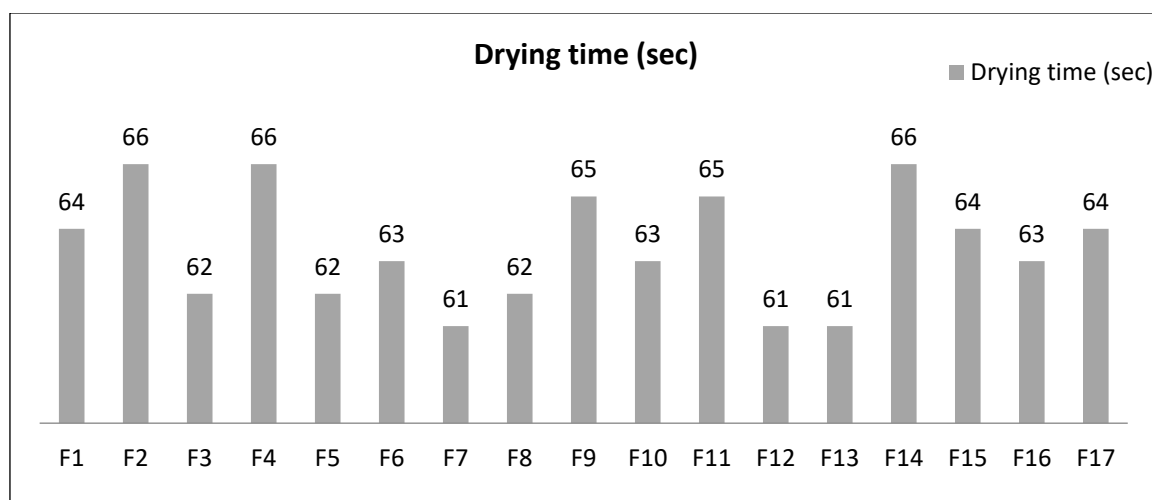
Drying Time

Drying time of the lacquers was found in range of 61–66 sec. Lower the drying time effectiveness increases. The data are shown in Graph 5.

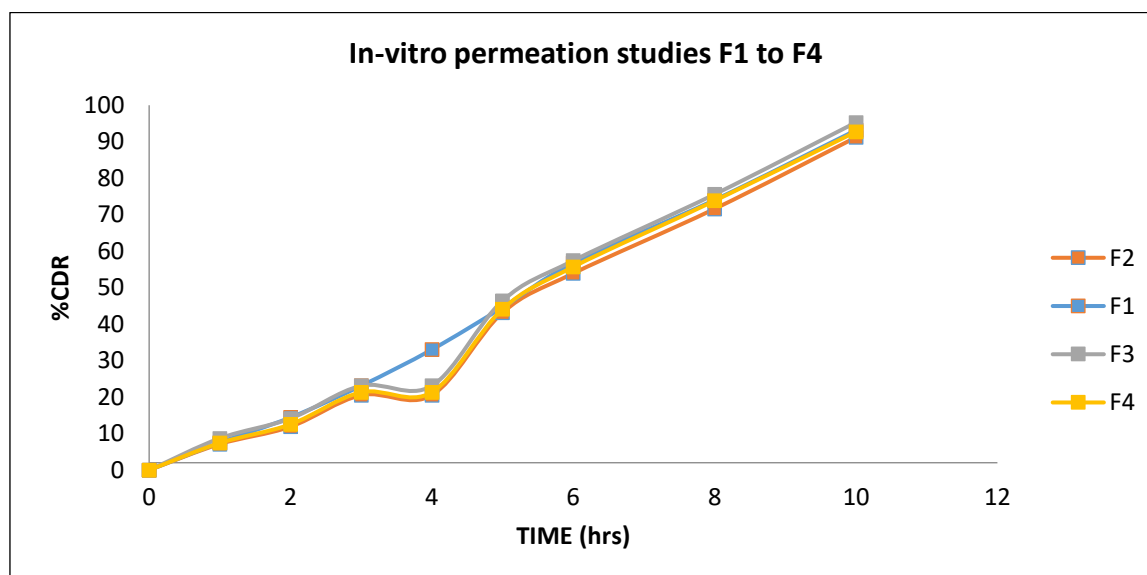
Diffusion Studies across Artificial Membrane

Diffusion studies of all the formulations were carried out using artificial membrane (cellophane membrane) for 10 h. The formulated batches F1–F17 consist of the permeation enhancer's Hydroxypropyl beta cyclodextrin, N-acetyl-L-cysteine and 2-

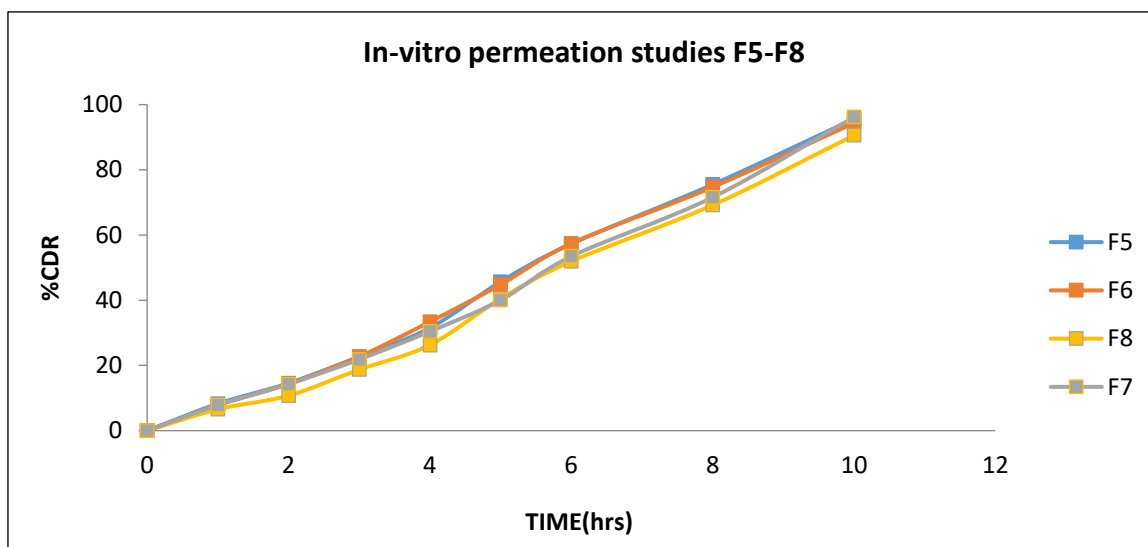
Mercapto ethanol in varying concentrations as suggested by the software. It was found that increase in concentration of HY- β -CD consequently increases the % CDR also (F3, F5, F7, F13). N-acetyl-L-cysteine and 2-Mercapto ethanol have the same mechanism of action, i.e., by cleaving the disulphide linkages of nail proteins and destabilize the keratin structure. It was found out that 3% w/v n-acetyl-L-cystine concentration along with 2.5% w/v of 2-mercapto ethanol gives the maximum % CDR (F7). It was observed that while varying the concentration of permeation enhancers, there was change in % CDR. In order to develop an optimum batch having high % CDR with low drying time and with no significant smell optimization technique was carried out (Graphs 6–9).



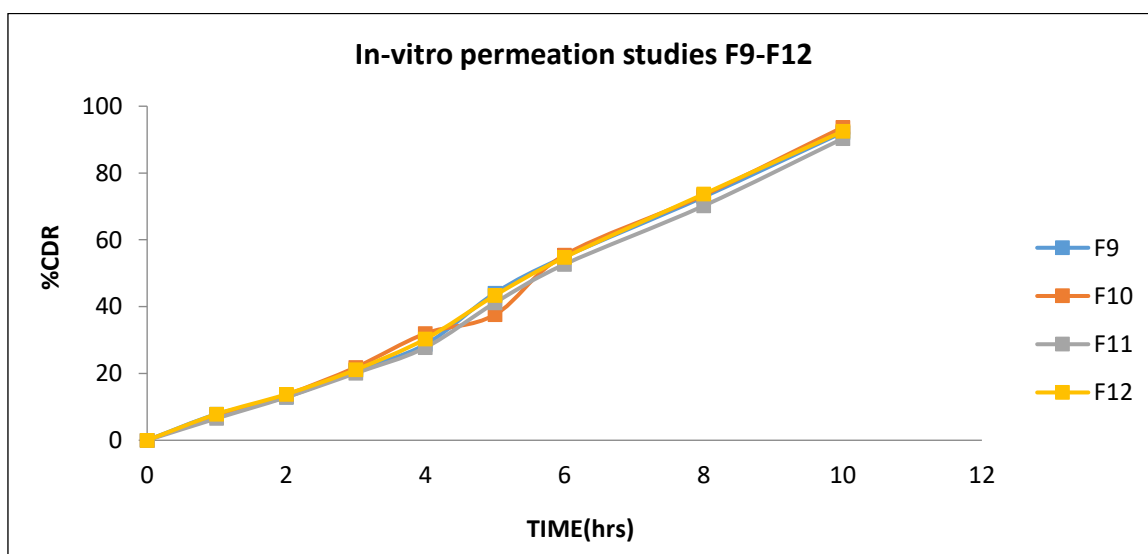
Graph 5: Drying Time.



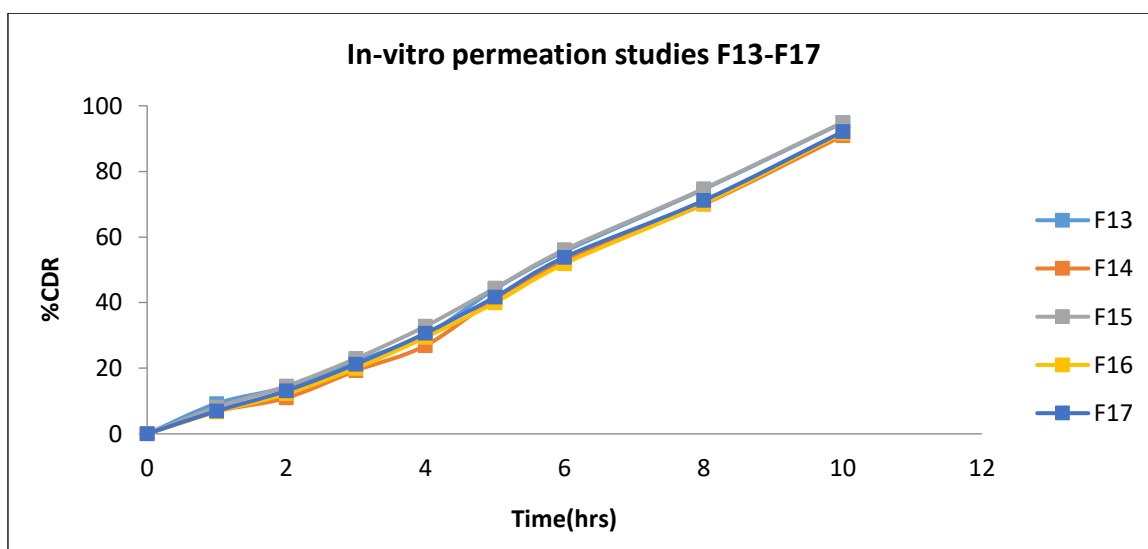
Graph 6: In-vitro Drug Release of F1, F2, F3 and F4.



Graph 7: In-vitro Drug Release of F5, F6, F7 and F8.



Graph 8: In-vitro Drug Release of F9, F10, F11 and F12.



Graph 9: In-vitro Drug Release of F13, F14, F15, F16 and F17.

Development of the Optimum Batch

Contour plots are two dimensional representations of the responses for the selected factors. Three dimensional surface plots for the obtained responses were drawn

based on the model polynomial functions to assess the change of response surface. The contour plot and the response surface plots of the significant interaction terms of the factors are given below (Figures 2–5):

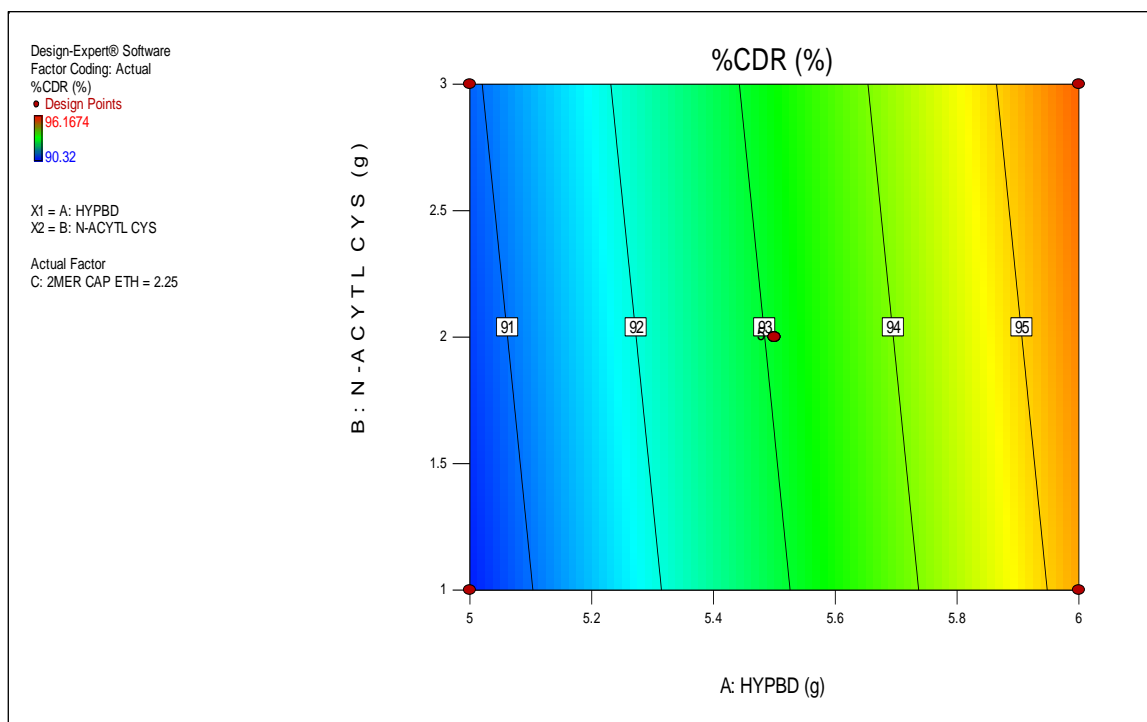


Fig. 2: Contour Plot for the Effect of Hydroxypropyl Beta Cyclodextrin, N-Acetyl-l-Cystene, 2-Mercapto Ethanol on %CDR.

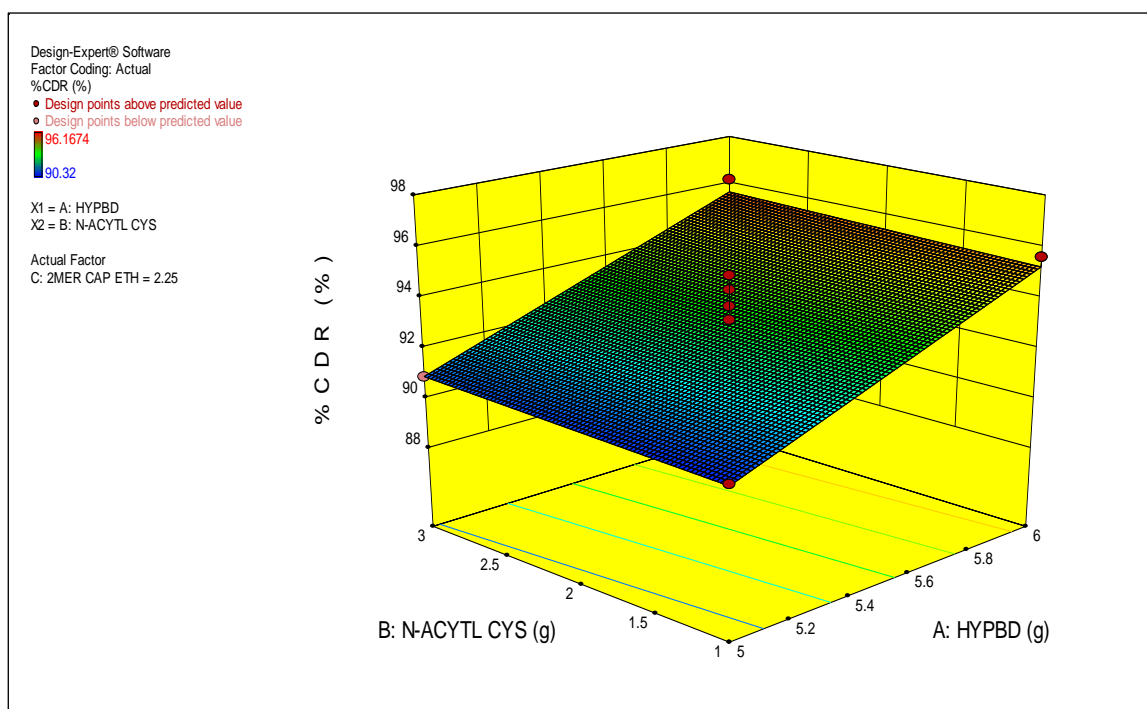


Fig. 3: Response Surface Plot for the Effect of Hydroxypropyl Beta Cyclodextrin, N-Acetyl-l-Cystene, 2-Mercapto Ethanol on %CDR.

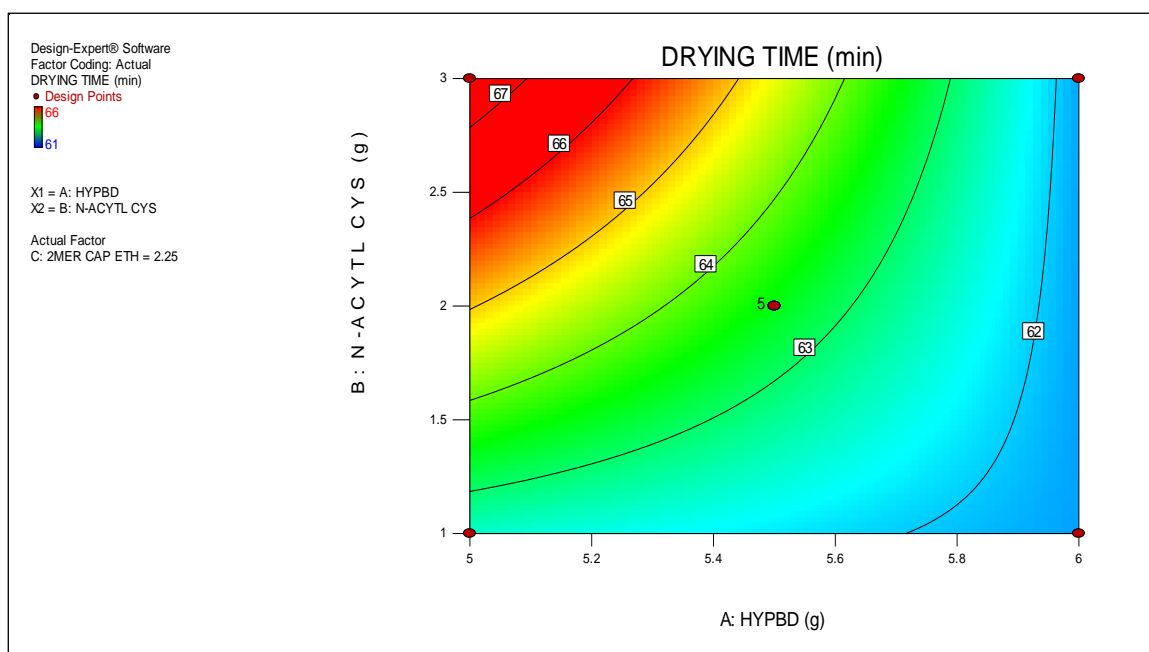


Fig. 4: Contour Plot for the Effect of of Hydroxypropyl Beta Cyclodextrin, N-Acetyl-L-Cystene, 2-Mercapto Ethanol on Drying Time.

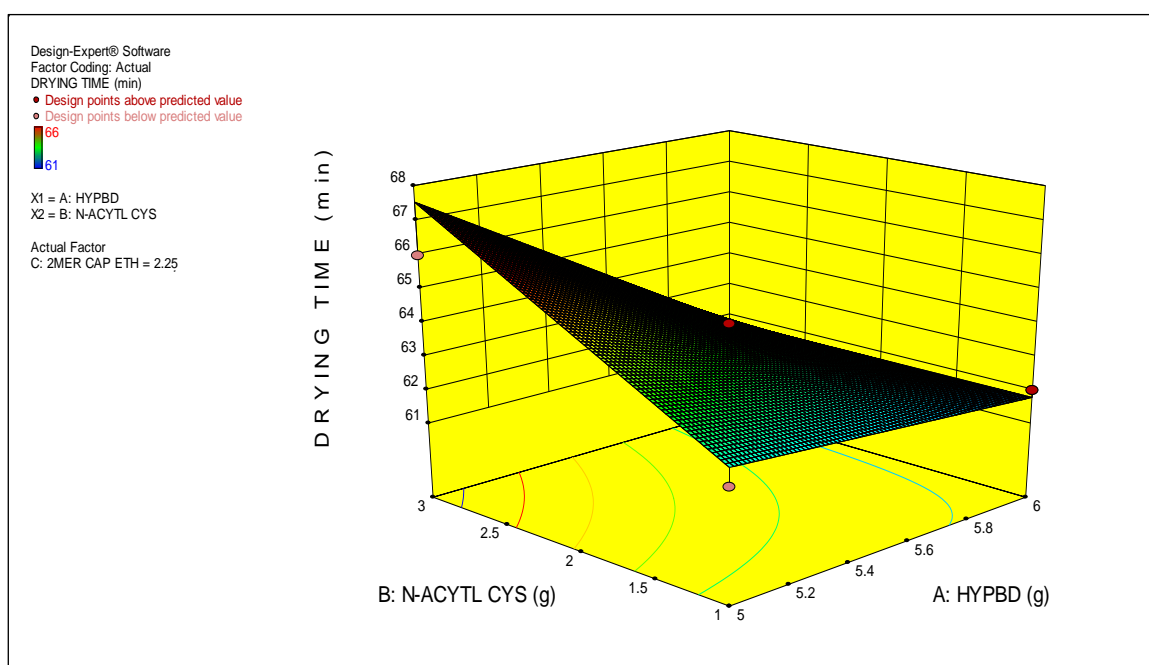


Fig. 5: Response Surface Plot for the Effect of Hydroxypropyl Beta Cyclodextrin, N-Acetyl-L-Cystene, 2-Mercapto Ethanol on Drying Time.

After generating the polynomial equation relating to the dependent and independent variables, the formulation was optimized for the responses. The desirable ranges of the responses were restricted to maximize the % CDR, minimize the drying time and since increases in concentration 2-Mercapto ethanol develops a bad smell, the desirability

for 2-Mercapto ethanol was set as minimum. The optimum values of the variables were obtained by the numerical analysis based on the criterion of desirability. Therefore a new batch of nail lacquer with the predicted levels of formulation factors was prepared to confirm the validity of the optimization procedure.

Based on the statistical evaluations, the software selected one optimum batch. The formula for the optimum batch is given below in Table 5.

Table 5: Formula for Optimum Batch.

Number	HP-B-CD (g)	N-Acyl Cys (g)	2-Mer Cap Eth (ml)	Predicted Values	
				% CDR	Drying Time (sec)
1	6	3	0.900	95.524	60.662

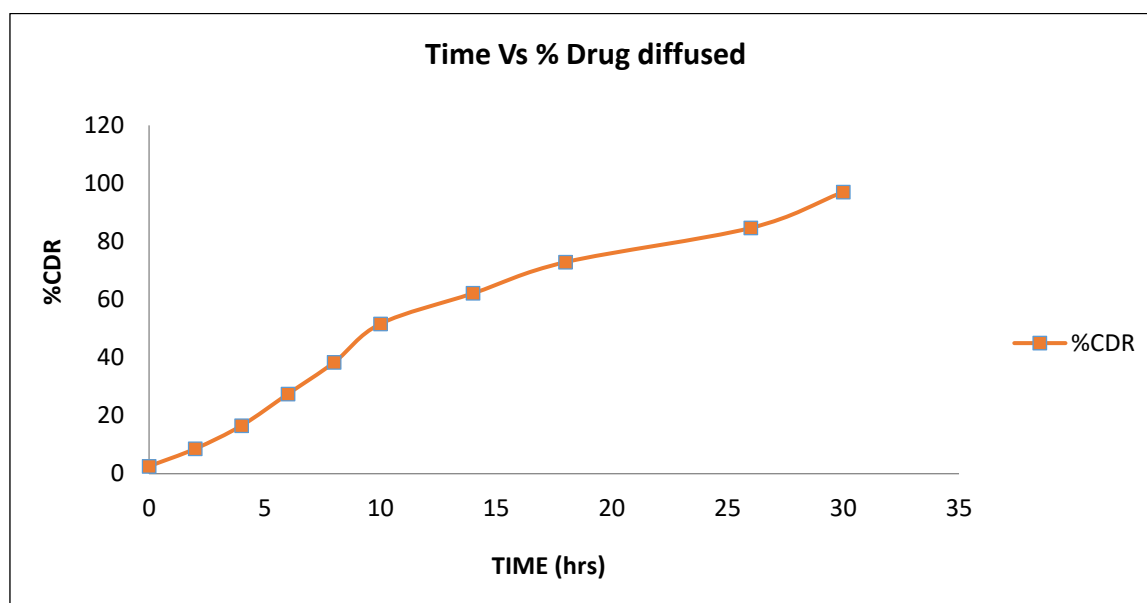
Evaluation of Optimized Nail Lacquer

Drying Time

Drying time of the lacquer was found to be 59.666 ± 1.529 sec (n=3)

In vitro Transungual Permeation Studies

In vitro testing of medicated nail lacquer was carried out using bovine hooves membrane which is a commonly accepted model for human nails. When compared to human nails, they have less dense keratin network. When incubated in water, it swells to a large extent due to lower content of half-cystine and disulphide linkages with respect to human nails. The study was carried out for 30 h. At the 30th h, 97.04533% of drug was permeated through the model. It shows that the optimized batch complies with the predicted % CDR. The data is shown in Graph 10.



Graph 10: In vitro Ungual Permeation Studies.

Determination of Zone of Inhibition

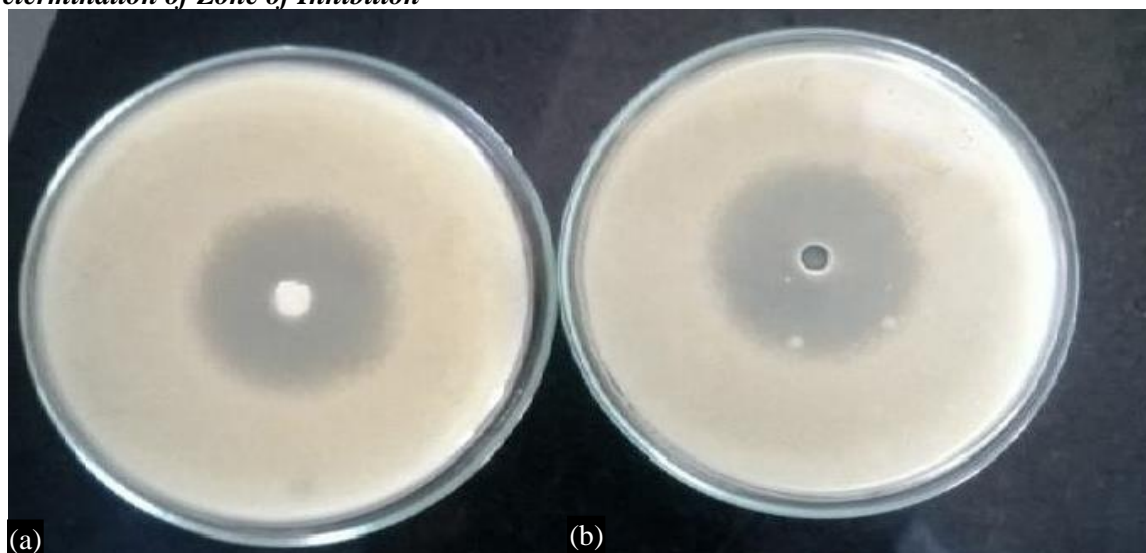


Fig. 6: Zone of Inhibition of Fluconazole.

The zone of inhibition for the optimized formulation was compared with the zone of inhibition of the pure drug (Figure 6). The zone of inhibition for pure drug (**B**) was found to be 26 mm and for optimized formulation (**A**) 24.5 mm, indicating that the formulation was sensitive to the microorganism *Candida albicans*.

Kinetics of *in vitro* Drug Release

The R² values suggested that the drug is released in a sustained manner over a period of time and shows zero-order model for the formulation. The release exponent (n) value in Peppas model is 1.366. It indicates that the drug transport mechanism is Super case-II transport.

Stability Studies

The optimized batch of nail lacquer was subjected to stability studies for a period of 60 days. The studies were carried out to verify the changes in characteristics of non-volatile content, drying time, gloss, smoothness of flow, water resistance, and drug content and diffusion across artificial membrane (Table 6).

Table 6: Stability Studies Data.

Optimized batch	Parameters	Before Stability Charging		After Stability Charging	
	Non-volatile content (%)	24.86		21.32	
	Drying time (sec)	60		65	
	Gloss	Satisfactory		Satisfactory	
	Smoothness of flow	Satisfactory		Satisfactory	
	Water resistance (g)	W1	W2	W1	W2
		5.75	5.82	5.72	5.84
	Drug content (%)	97.45		96.29	
	% CDR	97.45		96.88	

CONCLUSION

Film base was prepared using varying concentration of cellulose acetate and ethyl cellulose as film forming polymers. Out of that, 2% w/v cellulose acetate and 3% w/v ethyl cellulose shows better properties. The permeation enhancers were screened by nail plate hydration. Out of 19 permeation enhancers, three permeation enhancers, Hydroxy propyl beta cyclodextrin, N-acetyl-l-

cystene and 2-mercapto ethanol were selected based on the HEF₂₄ value. The formulation was optimized using Box-Behnken design keeping hydroxy propyl beta cyclodextrin, N-acetyl-l-cystene, 2-mercapto ethanol as independent variables. Various physicochemical parameters like nonvolatile content, drying rate, gloss, smoothness to flow, % CDR for nail lacquer was carried out. All the above parameters showed satisfactory results and were within the prescribed limits. Optimum formula which was suggested was formulated. The optimum batch shows % CDR as 97.0453, the release kinetics was zero order. Zone of inhibition and drying time was in the range with standard. The accelerated stability studies showed no significant difference in the evaluation parameters. This proved that the formulated nail lacquer was stable. It can be concluded that, the side effect hepatotoxicity when orally treated for onychomycosis using fluconazole can be avoided by using the fluconazole nail lacquer. The high permeation rate helps to reduce the treatment period.

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