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FORMULATION AND EVALUATION OF A MEDICATED NAIL LACQUER FOR THE TREATMENT OF ONYCHOMYCOSIS

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ABSTRACT

The purpose of the present investigation is to formulate and evaluate an antifungal nail lacquer for treatment of onychomycosis. A nail lacquer will be formulated, consisting of antifungal drug Miconazole nitrate, film forming polymers like nitrocellulose, plasticizer like propylene glycol and other required additives. An attempt will be done to enhance the transungual drug permeation of Miconazole nitrate using various permeation enhancers.

KEYWORDS

Miconazole nitrate, Permeation enhancer, Diffusion study and Permeation study.

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INTRODUCTON

Over the last decades the treatment of illness has been accomplished by administrating drugs to human body via various routes namely oral, parental, topical, inhalation etc. Every medical condition demands an accurate and appropriate treatment. As a matter of fact, the thought of resolving the patient's disease with least harm done to the patient's health is said to be the basic goal of any therapy. Moreover a good treatment technique necessitates thorough knowledge of pharmacokinetics and pharmacodynamics of the intended drug. Hence we struggle day to day relentlessly to research and better our techniques and technology to develop with the best mode of treatment

ensuring fast recovery as well as assuring safety of the patient.

Human nails do not have only protective and decorative role, but can also be considered as an alternative pathway for drug delivery, especially in nail diseases such as onychomycosis or psoriasis. These 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 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[1]. The inadequate research and knowledge regarding the properties of keratinized nail plate, the nail bed and the nail matrix caused a lesser focus on ungual system.

Horny structure 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 of decreased glow. It is due to the involvement of nail bed, reduction of blood supply, physical or chemical features of nail bed. As a result variety of diseases occurs. These diseases can be cured by achieving desired therapeutic concentration of drug by nail drug delivery system[2]. Major challenges of drug delivery to the nail (ungual drug delivery), with the lack of understanding of both the barrier properties of the nail and formulations to achieve enhanced ungual delivery restricting the efficiency of topical treatments for nail disorders. And also suffer from low patient compliance due to the long treatment periods (up to 4-8 months) which are required.

However, existing oral formulations typically contain large doses of active ingredients and also require long treatment, creating the potential for systemic toxicity especially in the liver. Thus, developing more effective methods for nail drug delivery is an important objective for the pharmaceutical industry[3].

MATERIAL AND METHODS[4-49]

Miconazole nitrate, HP- β- CD were procured from Yarrow chemicals, Mumbai, Salicylic acid from Nice chemicals Pvt. Ltd Cochin Ethyl cellulose, Kemphasol, Popatwadi, Mumbai, Sodium hydroxide, Potassium dihydrogen, Laboratory grade, Nice chemicals Pvt. Ltd Cochin. All the chemicals used were analytical grade.

Formulation Studies

Formulation of nail lacquer

The formulation trials were done as per formula given in Table No.1. The mixture of Miconazole nitrate and Nitrocellulose was dissolved in Ethyl alcohol in the required quantity using a magnetic stirrer at a constant speed. To above clear solution required quantity of 2-HP- β- CD, Salicylic acid, and propylene glycol were mixed thoroughly and made up to the volume to 100ml. The prepared nail lacquer was transferred to a narrow mouthed, plastic screw capped glass bottle.

EVALUATION OF NAIL LACQUER[3, 20-22]

Nonvolatile content

10 ml of sample was taken in a petri dish and initial weights were recorded. The dish was placed in the oven at 105^0C for 1hr, the petri dish was removed, cooled and weighed. The difference in weights was recorded. Average of triplicate readings was noted (Table No.2).

Drying time

A film of sample was applied on a petri dish with the help of a brush. The time to form a dry-to- touch film was noted with the help of stop watch (Table No.3).

Smoothness to flow

The sample was poured from a height of 1.5 inches into a glass plate and spread on a glass plate and made to rise vertically and visually observed for smoothness of film.

Gloss

Sample of nail lacquer was applied over the nail and gloss was visually seen, compared with marketed cosmetic nail lacquer.

Viscosity

Viscosity was determined using Brookfield Viscometer, model LVF at room.

Temperature using spindle No.3 at 20 rpm.

Adhesion

There are no quantitative evaluation tools available to assess the medicinal nail lacquer at this time. Hence an equipment designed in the Pharmaceutics Lab has been used to determine the adhesive property of nail lacquer. The instrument is a modification of chemical balance used in the normal laboratory as shown in Figure No.10. One pan of the balance was replaced with two stainless steel plates. In between the plates a film of 4 cm^2 was prepared and adhered. The equilibrium of the balance was adjusted by adding a weight to the right pan of balance. The force required to pull away the plates is recorded and compared with a commercial cosmetic nail lacquer sample.

Force of Adhesion = Mass x Acceleration due to gravity

= Kilogram. Meter/ $second^2$

= Newtons. Meter/$seconds^2$

$$\text{Adhesive Strength} = \frac{\text{Force of Adhesion}}{\text{Surface area } (m^2)} \quad (N)$$

Drug content estimation[49]

Nail lacquer equivalent to 200mg was dissolved in 50 ml phosphate buffer solution of pH 7.4. Then the solution was ultra sonicated for 15 mints. The resulting solution was filtered, made up to 100 ml with phosphate buffer solution of pH 7.4. From the above solution take 10ml and made up to 100ml with PBS of pH 7.4. Then the diluted solution was estimated spectrophotometrically at wavelength of 223 nm and determined the drug content.

Diffusion studies across artificial membrane[3, 20, 21]

Diffusion studies were performed by Franz diffusion cell using artificial membrane (cellophane) of 0.8µm. The membrane was soaked for 24hrs in solvent system and the receptor compartment was filled with solvent.

Nail lacquer equivalent to 200mg was applied evenly 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 for 20hrs. The 5ml aliquot of drug sample was taken at time intervals of 2hr, 4hr, 6hr, 8hr, 10hr, 12hr, 16hr and 20hrs and was replaced by the fresh solvent. Samples were analyzed by double-beam UV spectrophotometer as per method mentioned in drug content estimation. Each experiment was repeated thrice.

***In vitro* ungual permeation studies**[49]

Hooves from freshly slaughtered cattle, free of adhering connective and cartilaginous tissue, were soaked in distilled water for 24hrs. Membranes of about 1mm thickness were 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. Then the nail lacquer equivalent to 200mg was applied evenly on the surface of the nail membrane. The receptor compartment was filled with solvent phosphate buffer solution of pH 7.4, and the whole assembly was maintained at 37°C with constant stirring for 48hrs. The 5ml aliquot of drug sample was taken after a time intervals of 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48hrs and was replaced by the fresh solvent. The drug analysis was done by using double-beam UV spectrophotometer at 223nm.

Stability study

Stability studies of nail lacquers were carried out as per ICH guidelines. Samples were stored at temperature of 25±2 ^{0}C/60 ± 5% RH for 6months and 40 ± 2^{o}C/75 ± 5% RH for 1 month. Then the samples were analyzed for non -volatile content, drying time, gloss, smoothness of flow, drug content and diffusion across artificial membrane.

RESULTS AND DISCUSSION

All formulations showed desired film formation, smoothness of flow was good. Desired amount of nonvolatile matter (31-41%) was seen with complete evaporation of volatile matter leaving a thin film; the results were plotted in Table No.2. Drying time was found within 52 -127 sec. Except for F2, where it showed 127 sec, all formulations showed rapid drying rate. i.e. less than 60 seconds. The data's were mentioned in Table No.3.

Nonvolatile content

The non- volatile content of all formulations has been reported in the Table No.3, given below.

Smoothness to flow and Gloss

Both these parameters was found to be satisfactory as

can be observed from Figure. The nail lacquer poured onto the glass plate was found to spread and result in a uniform smooth film. The gloss of the applied lacquer was comparable with marketed cosmetic sample proving the cosmetic acceptance.

Viscosity

The viscosity of the sample ranged from 100 to 220 centipoise and it was observed that between 140 to 160 centipoise the product was clear and glossy. More over this viscosity range provided good adherence and flow property. Viscosity outside this range produces clouding and decreases gloss which will not be cosmetically acceptable (Table No.4).

Adhesive strength

The adhesive strength of the optimum batch was found to be comparable with marketed sample and hence can be expected to possess adequate adhesive strength on applied nail surface (Table No.5).

Percentage drug content determination

Percentage drug content for all the lacquers were found to be satisfactory and in between 86.25-99.01% which is reported in Table No.6. Highest % of drug content was found to be 99.01% (F11) and the lowest % of drug content was 86.25% (F3). Drug content more than 90% in the formulation shows the high amount of drug present in the formulation, ensuring that the methods of formulation and the ingredients selected are not affecting the stability of drug. High drug content also gives the assurance that, a good therapeutic outcome can be expected.

Diffusion studies across artificial membrane

Diffusion studies of all the formulations were carried out using artificial membrane (cellophane membrane - 0.8µm) for 48 hrs. The diffusion studies were conducted on all formulations as per given in Table No.7.

The first formulated batch F0 did not consist of any permeation enhancers and in vitro diffusion study revealed that only 27.10 % drug released till 48 hrs. Thus trials were planned to incorporate a permeation enhancer. Salicylic acid at concentrations of 5% (F1), 10% (F2), 15% (F3) and 20% (F4) was tried out. The diffusion studies revealed that only 64.18%, 65.10%, 68.34% and 69.10% respectively was released in 48 hours. It was clear that salicylic acid has improved the drug permeation due to its catalytic activity. But it was also found that the drug permeation was not still complete and further increase in salicylic acid concentration is not expected to improve permeation. Hence it was decided to select 15% w/v of salicylic acid as the optimum concentration.

To further improve drug diffusion it was decided to include 2-H- β-CD in concentrations of 5% (F5), 7.5% (F6) and 10% (F7) into formulations. The drug release and diffusion across membrane was found to improve in presence of 2-HP- β-CD. At concentration of 5%, 82.40% diffusion in 28th hour was observed. In case of F6, 89.0% diffusion was observed at 28th hour. It was also observed that as concentration of 2-HP- β-CD increased drug diffusion also improved drastically as clear from almost complete drug diffusion of 98.40% release in 20th hour with 7.5% concentration.

Though, inclusion of 2-H-β-CD has improved drug diffusion to 98.40%, it was observed that the release was found to be complete within 20 hours. Therefore to sustain the drug release over an extended period it was decided to include a rate controlling polymer ethyl cellulose at concentrations of 0.25% (F8), 0.5% (F9) and 0.75% (F10) and 1.0% (F11) into formulations. The result showed an extended and complete drug release of 96.80% at 28th hr. In F8 and 93.0 % till 36th hour in F9. In F10, a drug diffusion of 97.20% was observed at 40th hr. And finally when the concentration of ethyl cellulose was increased to 1% in F11, a drug diffusion of 98.12 percent which sustained over a period of 48 hours was achieved.

The formulation F11 was selected as the optimized nail lacquer formulation based on drug diffusion studies (Figure No.1-4).

***In vitro* ungual permeation studies**

To simulate and mimic diffusion study with that of *in vivo* conditions, i.e. across nail plate, a diffusion study across hooves obtained from freshly slaughtered cattle was done. There was no significant difference in diffusion and drug release data obtained across artificial and hoof's membrane. This study gives the assurance that a good *in vitro in vivo* correlation can be expected.

Stability studies

Stability studies were used to determine the shelf life

and storage condition of a product. In this investigation F11 were subjected to accelerated stability studies for a period of 1 month. Accelerated stability studies were performed in accordance with ICH guidelines with necessary modifications.

The studies were carried out to verify the changes in physical characteristics such as Non -volatile content, Drying time, % drug content, drug diffusion at three different conditions of higher temperature (40 ± 2^0C) for 1 month. The results are reported in Table No.8 and 9.

The evaluation of formulations after stability charging showed there was no significant change with respect Non -volatile content, Drying time % drug content and drug diffusion with respect to results obtained before stability charging. Thus it was concluded that the formulations were found to possess stability compliance requirements as per ICH guidelines.

Table No.1: Formulation of Nail Lacquer

S.No	Ingredients (%)	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Miconazole nitrate	2	2	2	2	2	2	2	2	2	2	2	2
2	Nitrocellulose	6	6	6	6	6	6	6	6	6	6	6	6
3	Salicylic acid		5	10	15	20	15	15	15	15	15	15	15
4	2-H- β-CD	…	…	…	…	…	5	7.5	10	10	10	10	10
5	Ethyl cellulose	…	…	…	…	…	…	…	…	0.25	0.50	0.75	1.00
6	Propylene Glycol	10	10	10	10	10	10	10	10	10	10	10	10
7	Ethanol q.s	100	100	100	100	100	100	100	100	100	100	100	100

Table No.2: Nonvolatile content of nail lacquers

S.No	Formulation code	Non-volatile Content (%)	Formulation Code	Non-volatile Content (%)
1	F0	33±0.38	F6	37±0.81
2	F1	33±0.38	F7	35±0.70
3	F2	41±0.81	F8	31±0.40
4	F3	39±0.40	F9	34±0.41
5	F4	37±0.81	F10	33±1.22
6	F5	35±0.71	F11	36±0.81

Drying time

Table No.3: Drying time of nail lacquers

S.No	Formulation	Drying time	Formulation	Drying time
1	Code	(sec)	Code	(sec)
2	F0	50	F6	56
3	F1	52	F7	59
4	F2	127	F8	55
5	F3	52	F9	59
6	F4	58	F10	58
7	F5	59	F11	56

Table No.4: Viscosity of nail lacquers

S.No	Formulation code	Viscosity	S.No	Formulation code	Viscosity
1	F1	100	7	F7	200
2	F2	111	8	F8	140
3	F3	122	9	F9	142
4	F4	133	10	F10	146
5	F5	184	11	F11	152
6	F6	198	12	---	---

Table No.5: Adhesive strength of nail lacquers

S.No	Formulation Code	Force of Adhesion (N)	Adhesive strength (N/m^2)
1	F11	0.5	12.5
2	Market Sample	0.6	15

Table No.6: Percentage drug content

S.No	Formulation	Drug content	Formulation	Drug content
1	Code	(%)	Code	(%)
2	F0	90.00	F6	89.35
3	F1	91.50	F7	90.10
4	F2	93.75	F8	98.0
5	F3	86.25	F9	98.22
6	F4	94.28	F10	97.55
7	F5	95.80	F11	99.01

Table No.7: Comparison of drug diffusion across artificial membrane and hoof's membrane

S.No	Time	Percentage Drug Release (µg/ml)	
		% drug diffused through artificial membrane	% drug diffused through hoof's membrane
1	0	0	0
2	2	12.82	14.50
3	4	27.12	20.90
4	6	28.31	26.45
5	8	32.72	36.75
6	10	46.25	47.90
7	12	50.21	56.72
8	16	58.65	60.45
9	20	60.20	65.80
10	24	68.11	72.55
11	28	70.22	80.60
12	32	78.85	85.05
13	36	84.15	89.25
14	40	88.85	92.30
15	44	90.25	95.01
16	48	98.12	97.45

Table No.8: Stability studies data of F11

S.No	Parameter	Initial	After
1	Non-volatile content	36±0.81	35±0.35
2	Drying time(sec)	56	58
3	Drug content	99.01	98.50

Table No.9: *In vitro* Diffusion profile of F11 upon stability studies

S.No	Time	Percentage Drug Release (µg/ml)	
		Before stability	After stability
1	0	0	0
2	2	12.82	10.60
3	4	27.12	24.90
4	6	28.31	26.45
5	8	32.72	30.25
6	10	46.25	39.95
7	12	50.21	45.75
8	16	58.65	52.55
9	20	60.20	58.81
10	24	68.11	62.50
11	28	70.22	72.05
12	32	78.85	76.80
13	36	84.15	81.25
14	40	88.85	90.53
15	44	90.25	92.20
16	48	98.12	97.75

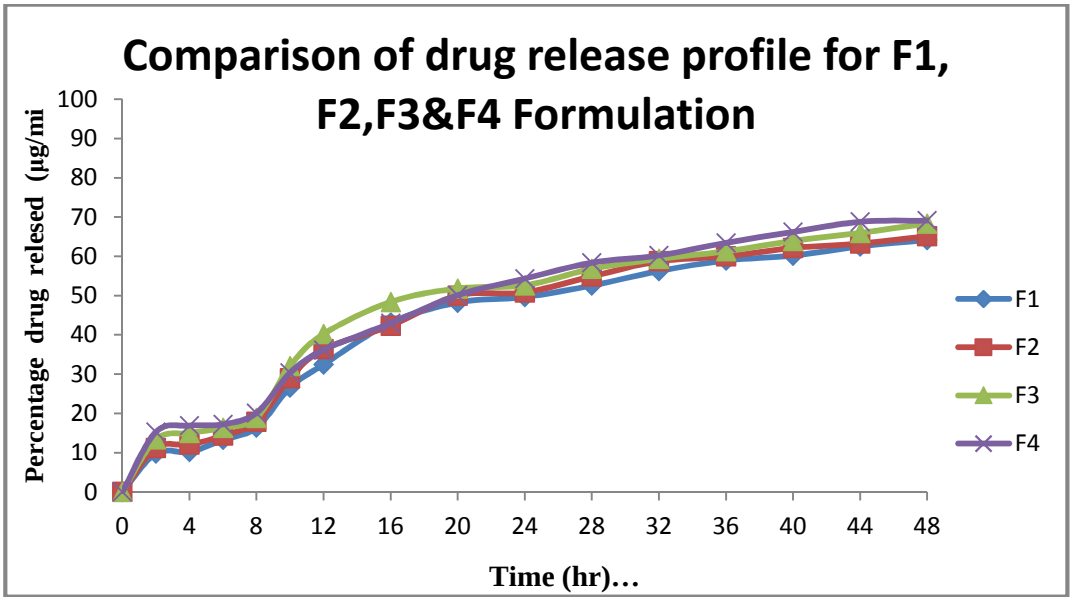

Figure No.1: Comparative Dissolution profile of F1 v/s F2 v/s F3 v/s F4

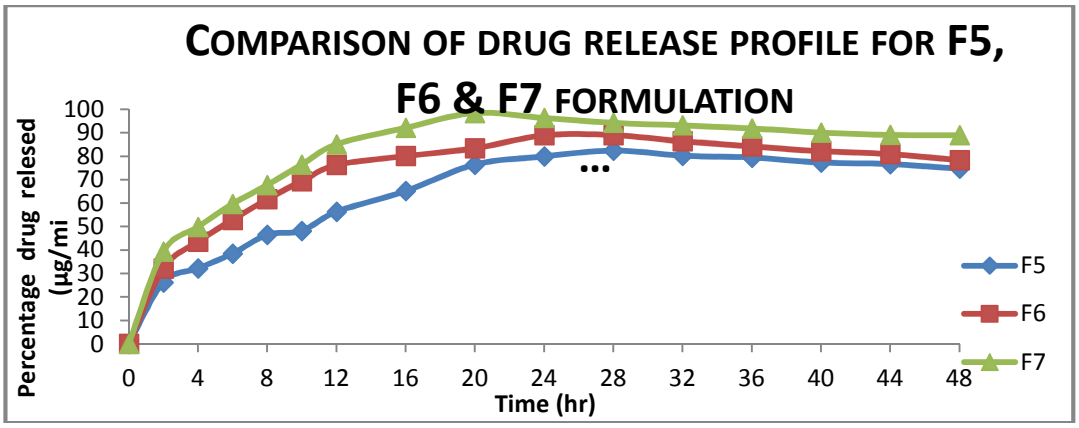

Figure No.2: Comparative Dissolution profile of F5 v/s F6 v/s F7

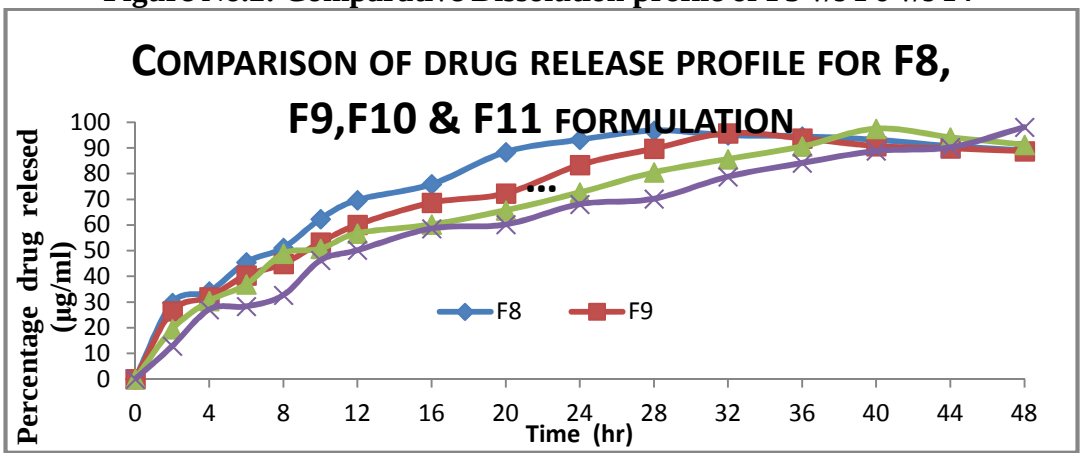

Figure No.3: Comparative Dissolution profile of F8 v/s F9 v/s F10 v/s F11

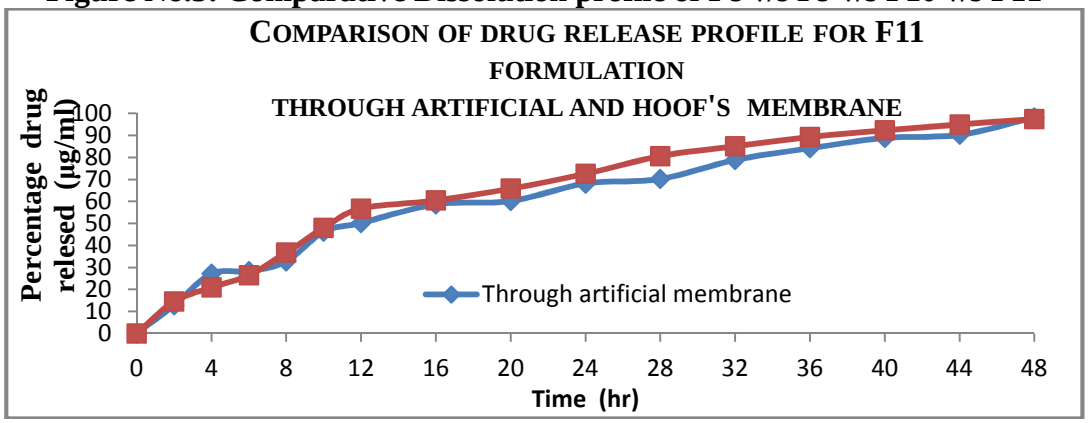

Figure No.4: Comparison of drug diffusion across artificial membrane and hoof's membrane

CONCLUSION

The purpose of the present investigation was to formulate and evaluate the Miconazole nitrate nail lacquer as an ungual drug delivery system for the treatment of onychomycosis. Miconazole nitrate was chosen as a model drug, the formulations were prepared with permeation enhancers (2-Hydroxypropyl)-β-cyclodextrin and keratolytic agent, Salicylic acid. Then, these lacquers were compared for drying time, nonvolatile content drug content, drug diffusion and anti -microbial studies. All formulations showed good film formation, drying time, smooth flow, and required volatile content. The stability tests showed that the formulations were stable at 40^0C for 1 month. From *in vitro* ungual permeation study a good

in vitro in vivo correlation can be expected. The results obtained from the *in vitro* studies indicate that formulation F11 showed a complete drug release which sustained over 48 hours. The F11 formulation had salicylic acid at concentration of 15% w/v as keratolytic agent and 10% w/v of **(***2-Hydroxypropyl*)-β-cyclodextrin as permeation enhancer. This indicates that the combination of permeation enhancer and keratolytic agent resulted in an improved permeation rate and also a complete and sustained drug release. The percentage non-volatile content of F11 formulation was found to be 36 ± 0.81. The desired amount of non-volatile matter was seen with complete evaporation of volatile matter. F11 formulation showed rapid drying rate. From Diffusion studies across artificial membrane, the inclusion of 2-Hydroxypropyl) -β-cyclodextrin to F11 has improved drug diffusion to 98.40%. The formulation F11 was selected as the optimized nail lacquer formulation based on drug diffusion studies.

Stability study data showed that there was no much change in the values after stability test. It was concluded that the formulations were found to possess stability compliance requirements as per ICH guidelines.

From the above studies, it can be concluded that medicated nail lacquers proved to be a better tool as a drug delivery system for the ungual drug delivery of an antifungal in the treatment of onychomycosis.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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