CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF NAIL LACQUER CONTAINING TIOCONAZOLE FOR TRANSUNGUAL DRUG DELIVERY SYSTEM

Deepak Singh Bisht*[1], Ganesh Kumar Bhatt[2], Preeti Kothiyal[3]

Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology, Uttarakhand Technical University, Dehradun (Uttarakhand), India.

Abstract:

In this present work, a medicated antifungal nail lacquer of tioconazole had been developed. The main objective of nail lacquer formulation was to provide a sustained release of medicament over extended period of time and reduce the frequency of administration by improving patient compliance. Topical delivery of nail diseases is limited by the poor permeability nail plate. Only few permeation enhancers are used to enhance the permeation, such as thioglycolic acid and urea hydrogen peroxide act by reducing the disulphide bonds in nail plate. In- vitro permeation studies were carried out across human nail plate by Franz diffusion cell using phosphate buffer pH 7.4 as medium. The percentage cumulative drug released was determined by UV spectrophotometer. FTIR studies revealed that drug and all excipients are compatible. The % drug permeated at 8hr through the nail was 64.93for tioconazole with thioglycolic acid and urea H_2O_2 respectively. As can be seen, significantly higher permeation was achieved in the presence of thioglycolic acid. Topical delivery of nail diseases is limited by the poor permeability of the nail plate but few ungula enhancers increase the nail permeability of topically applied tioconazole drug by reducing the disulphide bonds in nail plate, such as thioglycolic acid and urea hydrogen peroxide.

Key words: *Nail lacquer, Tioconazole, Thioglycolic acid.*

Corresponding author

Deepak Singh Bisht,
Shri Guru Ram Rai institute of Technology and Sciences,
Patel Nagar Dehradun
E mail- deepak.bisht41@rediffmail.com

QR code

Please cite this article in press as Deepak Singh Bisht et al , **Formulation and Evaluation of Nail Lacquer Containing Tioconazole for Transungual Drug Delivery System,** *Indo Am. J. Pharm. Sci, 2015;2(11).*

INTRODUCTION:

The major constrains of the preungual drug delivery (drug delivery through the nail) to nail is lack of understanding about barrier property related to the nail and formulations. Topical drug delivery system owes many advantages in case of anti fungal drugs such as it avoids hepatotoxicity, high tissue concentration which is required for the treatment of fungal infection of nails. Most of topical formulations in form of gels, lotions etc pose limitations such as removal by whipping, rubbing and less adherence of formulation to the affected site of nail [1].

Conventional nail lacquers are mostly used mainly for the cosmetic purpose. Nail drug delivery can be made as effective route for the treatment of fungal infections of nails. Human nail is a complex structure. It protects the nail bed and the parts which are under the nail plate filled with blood vessels. Medicated nail lacquer is an excellent alternative for the treatment of fungal infection of nails and high efficacy of drug can be achieved. It also provides a optimized and sustained release of drug by formation of an occlusive film which acts as "depot" after the application of lacquer on the nail [2].

Tioconazole is a broad spectrum anti fungal drug. It is a triazoles derivative, its chemical formula is 1-[2-[(2-Chloro-3-thienyl) methoxyl]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole.

The present work investigated the amount of Tioconazole released from different formulations containing different concentration of Thioglycolic acid and different proportions of Thioglycolic

acid and urea solution in H_2O_2 for treatment of onychomycosis. The best formulation was evaluated for anti fungal sensitivity test against the *Candida albicans.* Kinetics release studies as well as stability studies were carried out on the best formulation for evaluation of kinetic model

for release of drug through the formulation and to check the stability of formulation.

MATERIALS AND METHODS:

Tioconazole and Thioglycolic acid was obtained as a gift sample from Themis medicare Pvt. Ltd. Haridwar, India. Propylene glycol, Glycerine, Ethanol, Ethyl cellulose, Urea and Hydrogen peroxide was purchased from Central drug house Pvt. Ltd. Delhi (IND).

Tioconazole nail lacquer was prepared by simple mixing method. Wherein the Tioconazole concentration (1g) was kept constant. 4 formulations were prepared and given in Table 1. Formulations F1, F2, F3, F4 contained 1% of propylene glycol,ethanol, glycerine along with the different concentrations of Ethyl cellulose, Thioglycolic acid and Urea solution.

Preformulation Studies [6,7,8]:

Preformulation:

Testing is the first step in the rational development of dosage form of a drug. It can be defined as the investigation of physical and chemical properties if drug substances alone or in combination with excipients. The overall objective of preformulation studies is to generate information useful to formulator in developing stable and bioavaliable dosage form which can be mass produced.

Melting Point

The sample was loaded in to sealed capillary (melting point capillary) which was then placed in melting point apparatus. The sample was then heated and as the temperature increase the sample was observed to detect the phase change from solid to liquid phase. The temperature at which the phase changes occur gives the melting point.

Preparation of Calibration Curve of Tioconazole

A stock solution of 10µg of tioconazole was prepared in methanol and scanned by UV spectrophotometer (200-400nm) for the determination of λ max of tioconazole. For selection of media the criteria employed were sensitivity, ease of sample preparations, solubility of drug and cost of solvents and applicability of method to various purposes. An UV spectroscopic scanning run (200-400nm) was carried out to select the best UV wavelength for detection of tioconazole in methanol. The analysis was carried out using Distilled water as blank. Absorbance of tioconazole was determined.

Calibration Curve of Tioconazole:

Accurately weight 50 mg of drug was dissolved in 50 ml of methanol and thus 1000 mcg solution was prepared now from this different dilutions were made and different concentrations were prepared in the range of 1-25 mcg/ml of tioconazole in methanol for standard curve.

Drug - Excipient Compatibility Study:

The objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for its information. This can be confirmed by carrying out by infrared light absorption scanning spectroscopy studies (IR).Drug and polymer was mixed in the equal ratio and finally grounded and intimately mixed with approximately 100 mg of dry potassium bromide powder. Grinding and mixing can be done with mortar and pestle. The mixture is then pressed into a transparent disk in an evacuable die at sufficiently high pressure. Suitable KBr disks or pellets can often be made using a simpler device such as a hydraulic press. The base line correction was done using dried KBr. Then, the spectrum of dried

mixture of drug and potassium bromide was scanned from 2000cm^{-1} to 400 cm $^{-1}$.

Evaluation of Nail Lacquer [3]:

Nonvolatile Content:

1gm of sample was taken in a glass Petri dish of about 8cm in diameter. Samples were spread evenly with the help of tared wire.

Drying Time:

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

Smoothness of Flow:

The sample was poured to approximately 1.5 inches and easily spread on a glass plate and made to rise vertically.

Gloss:

Gloss of the film was visually seen, comparing it with a standard marketed nail lacquer formulation.

Water Resistance:

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 and increase in weight was calculated. Higher the increase in weight lowers the water resistance

***In vitro* Transungual Permeation Studies:**

Hooves from freshly slaughtered cattle, free of adhering connective and cartilaginous tissue, were soaked in distilled water for 24 h. Membranes of about 1mm 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 1.23 cm². Then the test vehicle equivalent to 200 µg was applied evenly on the surface of the nail membrane. The receptor compartment was filled with solvent (phosphate buffer, pH 7.4; and methanol, in the ratio of 4:1), and the whole assembly was maintained at 37°C with constant stirring (600rpm) for 12 h. The 5 ml aliquot of drug sample was taken after a time interval of 1h and was replaced by the fresh solvent. Each experiment was replicated at least thrice. The drug analysis was done by using single-beam UV spectrophotometer.

Stability Studies:

According to ICH guidelines at 40 ± 2°C/75 ± 5% RH sample was stored in stability chamber for one month. The sample was evaluated for non volatile content, drying time, gloss, and smoothness of flow, water resistance and diffusion across artificial membrane.

Kinetic Release Studies [4,5] :

The *in- vitro* release data were analysed by zero order, first order, Higuchi and Kosmeyers and Peppas equations.

Zero Order Release Kinetic: To study the zero order release kinetics the release data was fitted into the following equation.

$dQ/dt = Ko$

Where 'Q' is the amount of drug release, 'Ko' is the zero order release rate constant and't' is the release time. The graph is plotted percentage cumulative drug release (%CDR) verses time.

First Order Release Kinetic: To study the first order release kinetics the release rate data are fitted into the following equation.

$dQ/dt = K_1 Q$

Where, 'Q' is the fraction of drug release, 'K_1' is the first order release rate constant and't' is the release time. The graph is plotted log %CDR remaining verses time.

Higuchi Release Model: To study the Higuchi release model the release rate data are fitted into the following equation.

$Q = K_H t^{1/2}$

Where, 'Q' is the fraction of drug release, 'K_H' is the release rate constant and 't' is the release time. The graph plotted % CDR verses square root of time.

Kosmeyers and Peppas Kinetics: To study Kosmeyers and Peppas release kinetics the release rate data are fitted into following equation:

$Mt/M^{\infty} = KKP\ tn$ Where, Mt/M^{∞} is the 'fraction of drug release, 'KKP' is the release rate constant and 't' is the release time and 'n' is the diffusion exponent related to mechanism of drug release. The graph is plotted log %CDR verses time.

Formulation of Nail lacquer:

Preparation of Master formula.

Table 1: Formulation Plan for Tioconazole Nail Lacquer

Ingredients	F1	F2	F3	F4
Tioconazole(g)	1 g	1 g	1 g	1 g
Ethyl cellulose(g)	2 g	2 g	1g	1g
Propylene glycol(ml)	1 ml	1 ml	1 ml	1 ml
Glycerine(ml)	1 ml	1 ml	1 ml	1 ml
Ethanol(ml)	100 ml	100 ml	100 ml	100 ml
Thioglycolic acid(ml)	1 ml	2 ml	3 ml	4 ml
Urea Solution (1 gm in 1 m H_2O_2 (ml)	1 ml	2 ml	3 ml	4 ml

***F1- F2** = low viscosity and low permeability. **F3-F4** = high permeability with average viscosity.*

Preparation of Nail lacquer by Simple Mixing Method

Tioconazole nail lacquer (1% nail lacquer) was prepared by simple mixing method. Tioconazole concentration (1gm) was kept constant. 4 formulations were prepared F1, F2, F3, and F4 contained 1- 2% w/v of ethyl cellulose and 1 ml of glycerine along with the different concentrations of Thioglycolic acid.

Preformulation Studies

Identification of Drug by FTIR:

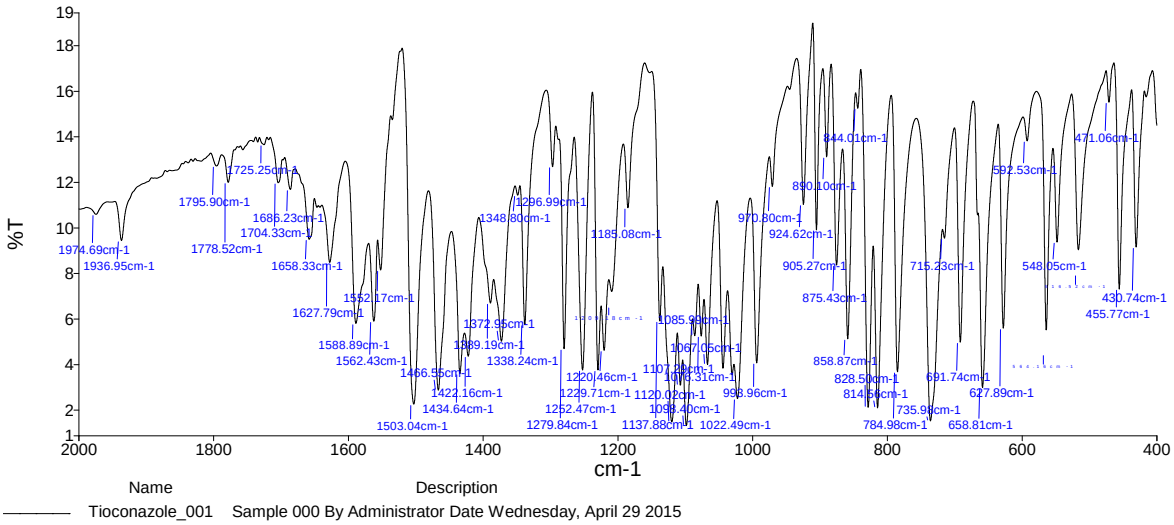

Fig 1: FTIR Spectrum of Tioconazole

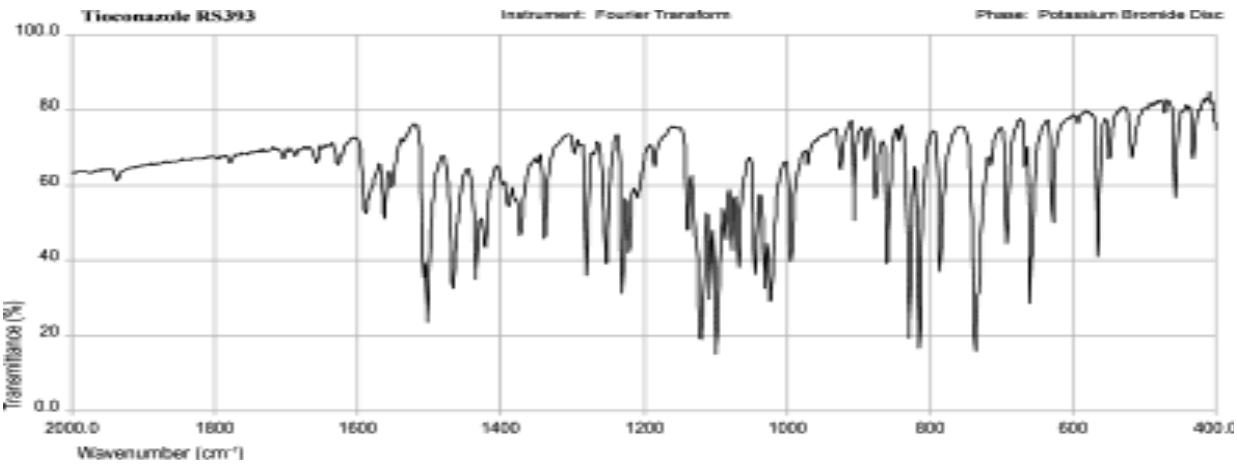

Fig 2: FTIR Spectrum of Tioconazole (with reference B.P. 2010).

RESULTS AND DISCUSSION:

Four formulations of Tioconazole were formulated using different drug polymer ratios. The formulation is subjected to evaluation parameters like drug content, non- volatile content, drying time, smoothness of flow, gloss, water resistance, *in- vitro* permeation studies,stability, kinetic release studies.

Table 2: Characteristics Peaks of Tioconazole

S.No.	Reference peaks (cm^{-1})	Obtained peaks (cm^{-1})	Functional Group	Stretching/Bending
1.	1675-1600	1627.79	C=C(Alkenes)	Stretching
2.	1470-1430	1466.55	C-H	Deformation
3.	1335-1250	1279.84	C-N	Stretching
4.	1450-1400	1434.64	C=C	Stretching
5.	800-600	627.89	C-Cl	Stretching

The comparison between the peaks of two graphs shows that the characteristics peaks of tioconazole (taken from B.P.) was found to be similar to the given drug sample, which shows that the drug is Tioconazole.

Organoleptic Characteristics:

The colour, order and taste of the drug were characterized and recorded using descriptive terminology, the results are shown in Table No. :3.

Table 3: Results of Organoleptic Properties

S.No.	Properties	Results
1.	Description	Solid
2.	Colour	White to off white
3.	Odour	Odourless
4.	Taste	Tasteless

Solubility:

Tioconazole is soluble in ethyl acetate, chloroform and very soluble in methanol, ethanol as shown in Table No : 4.

Table 4: Results of Solubility Studies

S.No.	Solvent	Solubility	Solubility(mg/ml)
1.	Water	Very slightly soluble	0.2
2.	Methanol	Soluble	48
3.	Ethanol	Soluble	42
4.	Chloroform	Soluble	22
5.	Ethyl acetate	Soluble	28

Melting point determination:

The melting point of tioconazole was found to be 168-170° C. This value is same as that of the literature citation 170-172° C.

Table 5: Results of Melting Point Determination

Observed melting point	**168-170°C**
Reported melting point	170-172°C

Partition Coefficient Determination:

The partition coefficient of drug was found to be 5.121.

Spectral Studies

Drug- Excipient Compatibility Study:

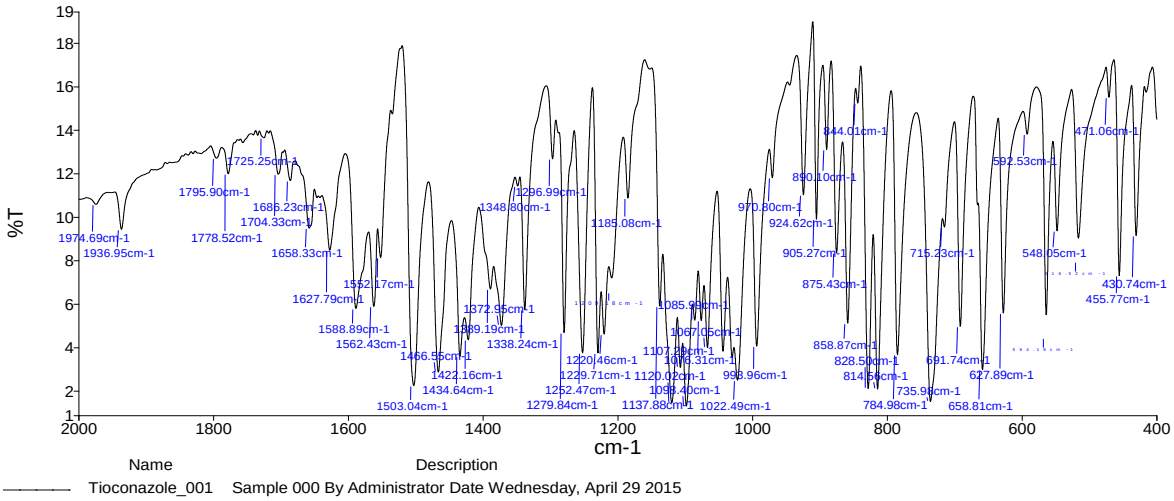

Fig 3: FTIR Spectrum of Tioconazole

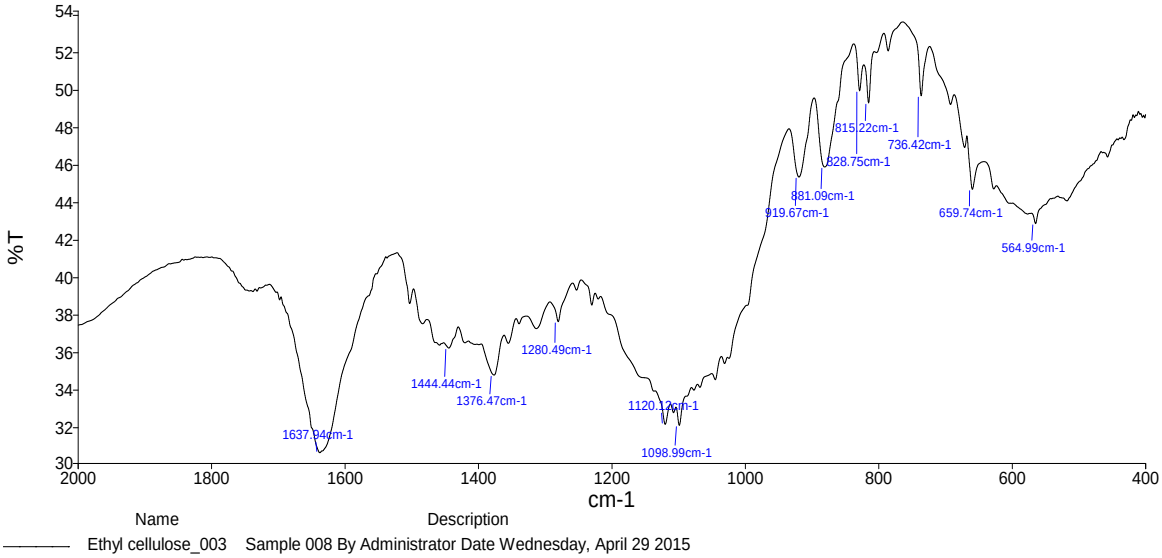

Fig 4: FTIR Spectrum of Ethyl cellulose (Polymer)

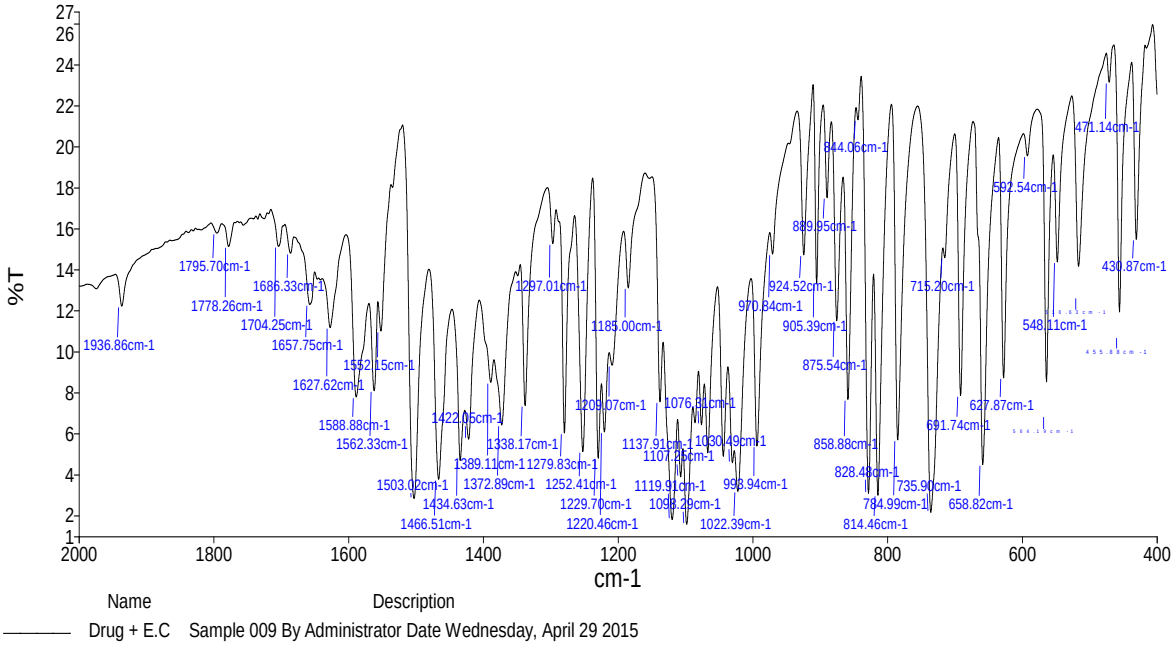

Fig 5: FTIR of Tioconazole + Ethyl cellulose (Polymer)

Table 6: Characteristics Peaks of Tioconazole and Ethyl Cellulose Physical Mixture.

S.No.	Peaks(cm^{-1}) of drug	Peaks(cm^{-1}) of drug + Ethyl cellulose	Functional Group	Stretching/Bending
1.	1627.79	1627.62	C=C(Alkenes)	Stretching
2.	1466.55	1466.51	C-H	Deformation
3.	1279.84	1279.83	C-N	Stretching
4.	1434.64	1434.63	C=C	Stretching
5.	627.89	627.63	C-Cl	Stretching

The drug-polymer interactions shows that there was no major shifts in the absorption bands(peaks) of in presence of polymer and it was observed that all the characteristics peaks of drug is present in the combination of drug and polymer spectra indicating the compatibility of drug with the polymer used.

Preparation of Calibration Curve of Tioconazole

Determination of λ_{max} of Tioconazole:

UV absorption spectrum showed λ_{max} to be 240nm. The graph of absorbance v/s concentration for tioconazole was found to be linear in the concentration range of 1-25 mcg/ml at 240 nm.Hence, the drug obeys Lambert -beer's law in this range. Fig. 6 shows UV spectrum of Tioconazole and Fig. 7 shows the calibration curve of tioconazole in methanol.

The calibration curve was prepared and results were shown in Table 7..

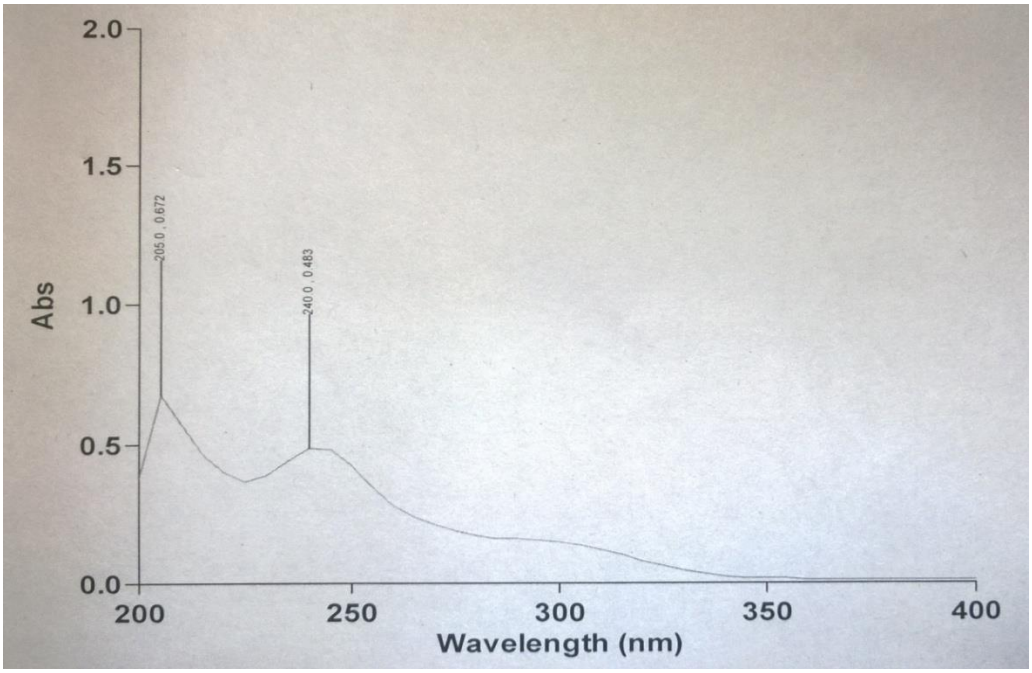

Fig 6: UV Spectrum of Tioconazole

Wavelength of maximum absorption (λ_{max}) in methanol was found to be 240 nm.

Table 7: Data for calibration Curve of Tioconazole in Methanol

S.No.	Concentration(mcg/ml)	Absorbance(λ =240)
1.	0	0
2.	5	0.238
3.	10	0.483
4.	15	0.644
5.	20	0.822
6.	25	0.978

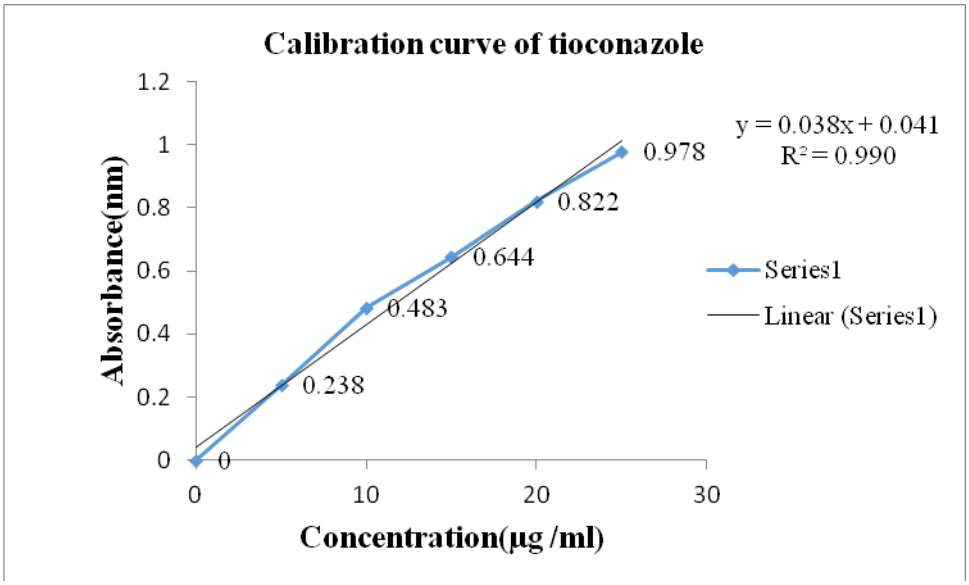

Fig 7: Calibration Curve of Tioconazole.

Line of Equation : y = 0.038x + 0.041
Beer's Range: 1-25 mcg/ml
R2 Value: 0.990
λ_{max} : 240 nm

Evaluation of Nail lacquer

Gloss

Gloss of nail lacquer was evaluated by comparing with the marketed product. It was found to be satisfactory when compared to the marketed product.

Smoothness of Flow

Smoothness of flow for formulation F1, F2, F3 and F4 was found to be good as compared to marketed formulation.

Drying Time

Drying time for formulation F1 to F4 was found between 64 to 70 secounds. It was found that as the polymer concentration increases the drying time increases respectively shown in table8.

Non- Volatile Content

The Non- volatile content of different formulation F1 to F4 was calculated and the Non- volatile content was found to be in range of 20.2 to 20.6. The results are shown in Table 9.

Water Resistance Test for Nail Lacquer

From the water resistant test, it can be seen that as the polymer concentration increases the water resistance increases and the polymer concentration decreases the water resistance decreases. Formulation F1, F2 showed lower water resistance as compared to F3and F4 shown table 10..

Table 8: Drying Time

S.No.	Formulation	Drying time
1.	F1	64
2.	F2	65
3.	F3	68
4.	F4	70

.

Table 9: Non- Volatile Content of Nail Lacquer

Formulation code	Non- volatile content (%)
F1	20.2 ±0.15
F2	20.3±0.05
F3	20.6±0.25
F4	20.3±0.05

Table 10: Water Resistance Test for Nail Lacquer

Formulation code	W_1(g)	W_2(g)	Difference in weight(g)
F1	8.25	8.43	0.18
F2	8.25	8.44	0.19
F3	8.25	8.45	0.20
F4	8.25	8.45	0.20

W_1 & W_2 are weight of glass slide along with nail lacquer before and after dipping in water respectively.

***In- Vitro* Permeation Study:**

The *in- vitro* permeation study on all formulation of Tioconazole was carried out in Franz diffusion cell pH 7.4 buffer.The *in -vitro* drug release of all formulation F1 to F4 are shown in Table. The cumulative release of drug was determined up to 8 hrs for formulation F1, F2, F3, F4 was 52.48, 53.13, 60.78, 64.93 respectively.

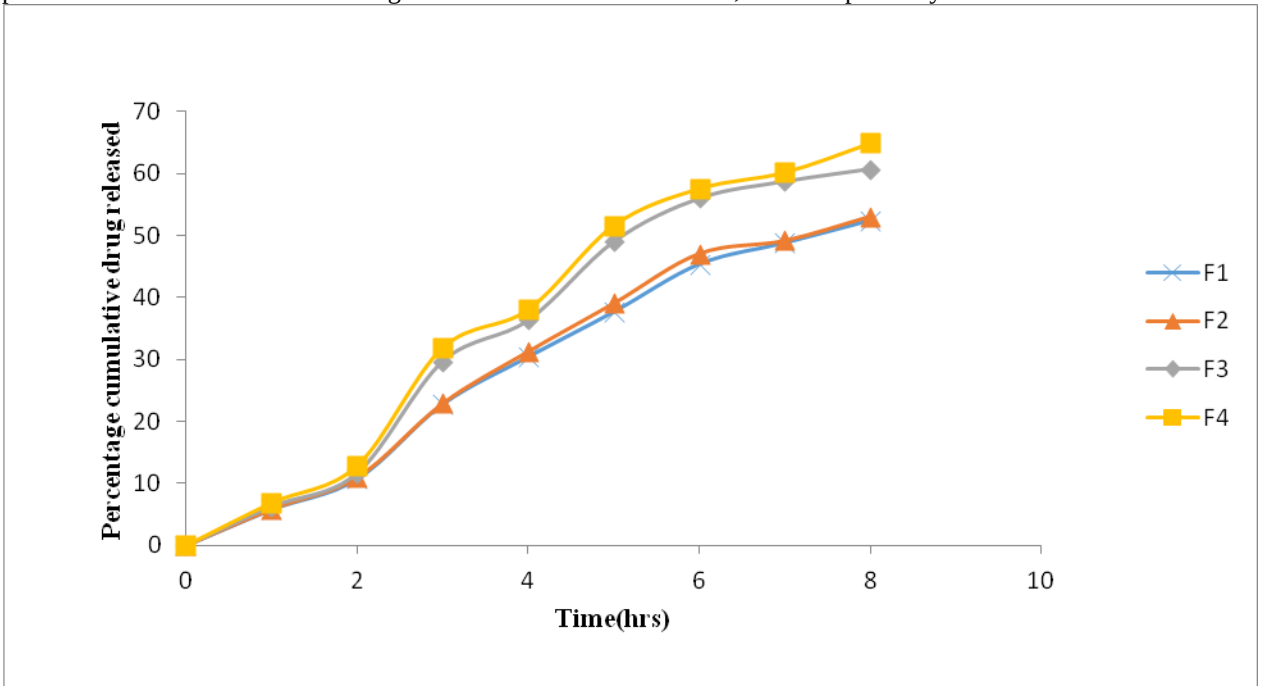

Fig 8 : Zero Order Release Plot of Tioconazole Nail Lacquer

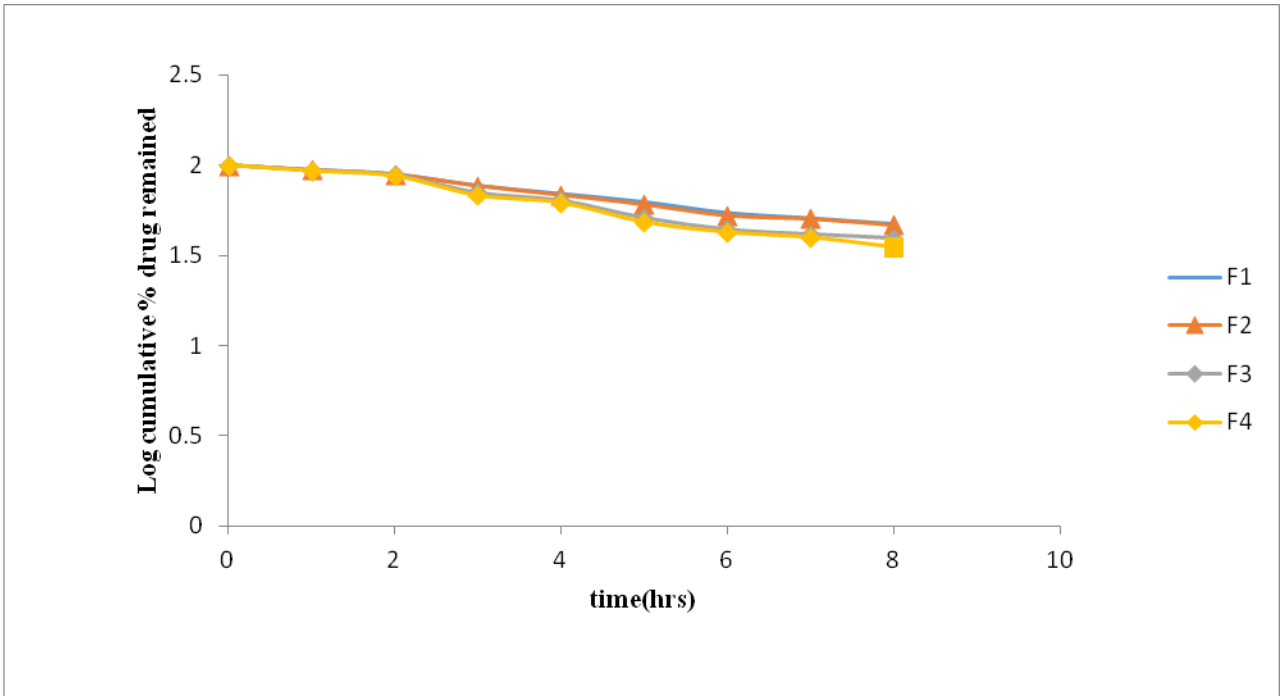

Fig 9 : First Order Release Plot of Tioconazole Nail Lacquer

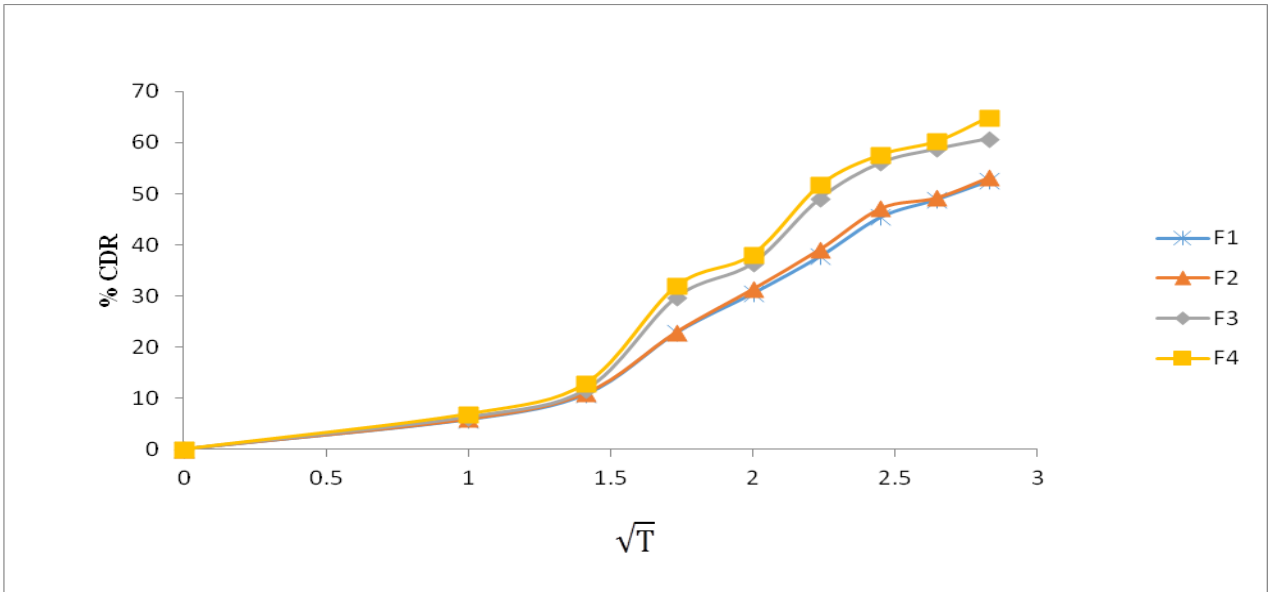

Fig 10: Higuchi Plot of Tioconazole Nail Lacquer

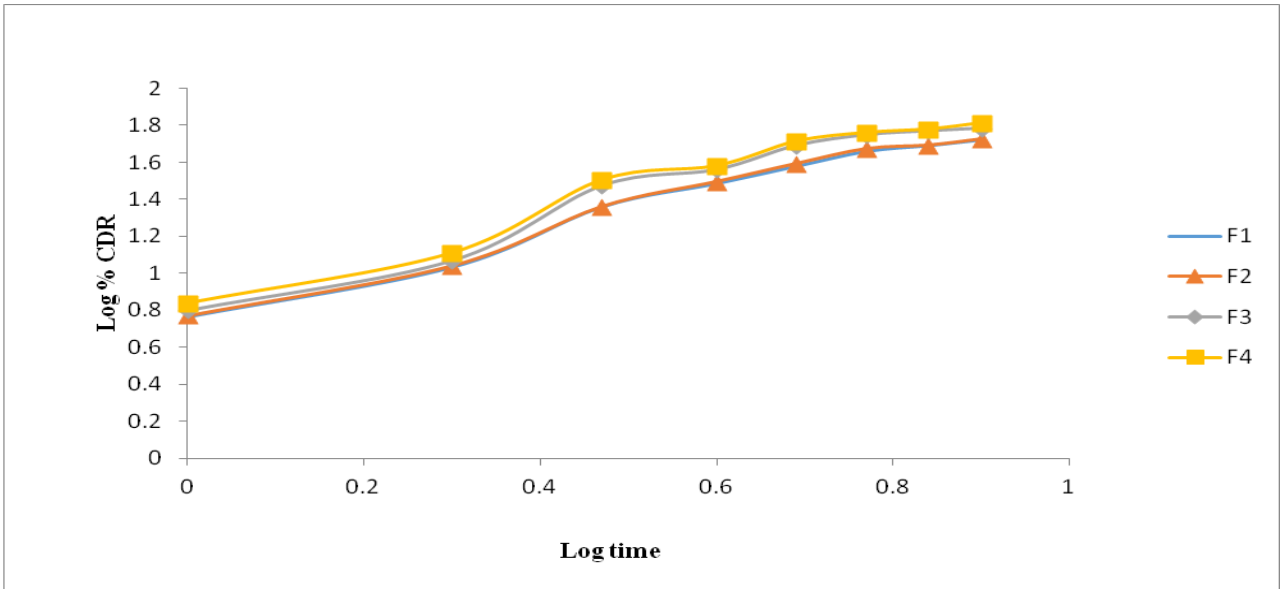

Fig 11 : Korsmeyer Peppa's Plot of Tioconazole Nail Lacquer

Mathematical Modeling:

The data obtained from *in- vitro* permeation studies was treated by various conventional mathematical models (zero order, first order, Higuchi and Korsmeyer- peppa's) to determine the release mechanism from the designed nail lacquer formulations. Selection of a suitable release model was based on the values of R^2 (correlation coefficient), k (release constant) obtained from the curve fitting of release data. In -vitro drug release data of all four formulations F1 to F4.

The regression coefficient of the all four formulation F1 to F4 is shown in Table 11. It was found that all the formulations follows the first order kinetics. The regression coefficients for the all formulations F1 to F4 of Higuchi plot was found to be almost linear.

Table 11: Model Fitting Release Profile of Formulation F1 to F4

Formulation code	Zero order	First order	Higuchi model	Best fit release mechanism
F1	0.982	0.990	0.914	First order
F2	0.978	0.986	0.913	First order
F3	0.960	0.974	0.906	First order
F4	0.964	0.981	0.912	First order

CONCLUSION:

FTIR studies revealed that there is no chemical interaction between the drug and polymer used.

The prepared formulations were subjected to different evaluation parameters such as drying time, non – volatile content, water resistance, smoothness of flow, evaluation of gloss, drug content,, *in – vitro* permeation studies,, drug release kinetic studies. From the evaluation data it was found that F4 formulation (4%w/v ethyl cellulose, 4%v/v Thioglycolic acid, 4% Urea Solution) was best formulation. It was found that penetration enhancers concentration increases, percentage drug released also increases. Drug release kinetics revealed that the release from formulations was by zero order and mechanism of release was by Higuchis model. Short-term stability studies of optimized formulations indicate that there were no significant changes in the drying time, drug content and percentage drug release values after 30 days of storage at 40±2 ºC with 75±5% RH.

REFERENCES:

1. Patel RP, Naik SA, Patel NA, Suthar AM: Drug Delivery across human nail. International Journal Of Current Pharmaceutical Research 2009; 1(1): 1 – 7.

2. Sabreen J, Divyakumar B, Kiran B: Preungual drug delivery systems of terbinfine hydrochloride nail lacquer. Asian Journal Pharmaceutical 2008; (2): 53-06.

3. Azharuddhin M, Suresh BH, Shabaraya AS, Prasad NGZ: Preparation and in – vitro evaluation of Antifungal Nail lacquer. International Journal of Universal Pharmacy and Bio Sciences July – August 2013; 2(4): 78 – 85.

4. Preethi M, Prathima S, Venkata RR, Sadanandam M: Formulation and evaluation of Duloxetine Hydrochloride delayed release enteric coated capsules: International Journal Of Pharma and Bio Sci. June – September 2011; 2(3): 52 – 72.

5. Bramankar DM, Jaisawal SB: Biopharmaceutics and pharmacokinetics-A treatise. 2nd edition. 347 - 48.

6. Simler, R., Walsh, G., Mattaliano, R.J., Guziewicz, N., and Perez-Ramirez, B. (2008). Maximizing Data Collection and Analysis During Preformulation of Biotherapeutic Proteins. BioProcess International vol. 6(10), pp. 38-45.

7. Subramanyam CVS, Text book of physical Pharmaceutics, thoroughly revised and enlarge;3rd Edn; Vallabhprakashan, NewDelhi, 124.

8. BioPharm International, "Guide to Formulation, Fill, and Finish," The BioPharm International Guide, 2004.