FORMULATION DEVELOPMENT AND EVALUATION OF NAIL LACQUER OF POSACONAZOLE FOR TREATMENT ONYCHOMYCOSIS

Patel Namrata Ashwinbhai[1], MR. Ajay Talele N*[2], DR. ANURADHA P. PRAJAPATI*[3], DR. SACHIN B. NARKHEDE.*[4]*

[1] M. Pharm, Department of Pharmaceutics, Smt. B.N.B Swaminarayan Pharmacy College, Gujarat India.*

[2] Assistant Professor, Department of Pharmaceutics, Smt. B.N.B Swaminarayan Pharmacy College, Gujarat India.*

*[3]*Head of department, Department of Pharmaceutics, Smt. B.N.B Swaminarayan Pharmacy College, Gujarat India.*

*[3]*Principle, Smt. B.N.B Swaminarayan Pharmacy College, Gujarat India.*

ABSTRACT

The aim of the study was to formulate and develop the nail lacquer of Posaconazole for treatment of onychomycosis. Posaconazole belong to class of triazole antifungal agent. Posaconazole exhibits broad-spectrum antifungal activity against a variety of yeasts and moulds including species of Candida albicans, majority used for the treatment of onychomycosis. Posaconazole act as an inhibitor of the enzyme lanosterol 14α- demethylase, which catalyses an essential step in ergosterol biosynthesis. This particular drug had been utilized in treatment of onychomycosis. Recently the use of nail lacquer has been proposed for this transungual drug delivery. Nail lacquer are used in finger nail and toe nails of human beings. Drugs like amorolfine and ciclopirox have been already marketed as nail lacquer for the treatment of onychomycosis. Posaconazole has low solubility and high permeability in order to treat disease formulation have been approach to modified dosage form as per need. Solvent casting method can be employed for preparation of nail lacquer.

Keyword: *Posaconazole, antifungal, nail lacquer, nitrocellulose, in-vitro diffusion.*

1. INTRODUCTION

1.1 Introduction to disease

Onychomycosis is defined as a fungal infection affecting nails of finger or toes resulting in thickening, discoloration and separation from the nail bed. Any component of the nail unit, including the nail plate, nail matrix, and nail bed can be affected. The term “onychomycosis” is derived from the Greek words “onyx” meaning nail and “mykes” meaning fungus. Onychomycosis affects about 10% of the common population but is more prevalent in adults.[1] [2] and [3].

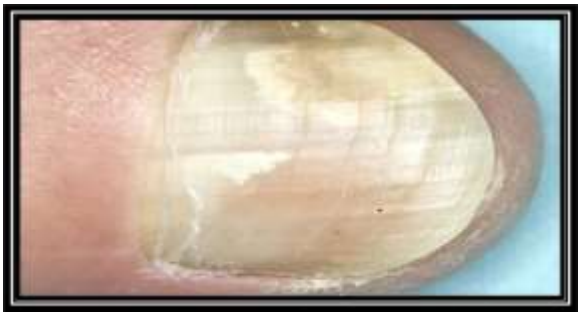

Fig-1: Onychomycosis

1.2 Types of onychomycosis

Onychomycosis diseases are classified clinically as:

- Distal and lateral subungual onychomycosis
- Superficial white onychomycosis
- Proximal subungual onychomycosis
- Candidal onychomycosis
- Total dystrophic onychomycosis

2. Nail lacquer

Nail polish or nail varnish is used for people fingernail or toenail to decorate and/or protection the nail plate. Conventional nail lacquers have been applied as cosmetics since a large duration for beautification and protection of nails. Topical nail preparation like lacquer, enamel and varnish are integral part of today's beautification curative. It is help for defense to the nail plate, but most significantly it maximizes their glowing, imparting color. Formulation of active objects, large tissue concentration for capacity for the treatment of nail fungal disease. The medicated drug is colour less and non-glossy to be applied for male patients, and more significant the drug is produce from the film so it can penetrate in to the nail the drug consisting polymer film may be considered as a matrix type-controlled release the drug are closely spread with polymer and predicted the spread drug in polymer film before it is produce. [4] [5].

2.1 Advantages of nail lacquer

- It cannot be easily separated through rubbing or washing
- In mixing, the effectual is large lasting, once using of lacquer give defence for once week.
- Produce and rate of diffusion can be made optimal by choosing the lacquer preparation (solvents, polymer and plasticizer).
- Formulation is easily as equivalence to oral dosage form.
- Lower or no systemic adverse effect.
- Regarding nail pharmacokinetics a lot of less portion of oral dose arrives nails.

2.2 Disadvantages of Nail lacquer

- Rashes associated to side effect that is erythema of proximal ail fold were presentation more often.

- Another side effectual which were thought to be normally related consist nail disorder that are shape change, irritation, ingrown toe nail and discoloration.

2.3 Constituent of Nail lacquer

- Film Formers
- Resins
- Plasticizers
- Solvents
- Pigments
- Suspending agents

2.4 Mechanism of Nail lacquer

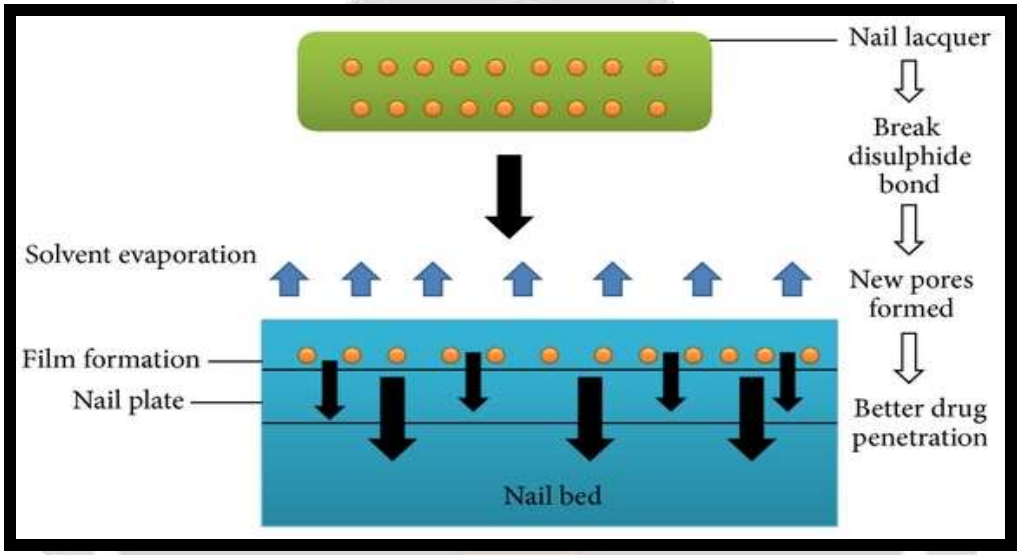

Fig-3: Mechanism of Nail lacquer

The nail lacquer as a film forming system is directly applied to the nail or skin and forms a thin, transparent film after solvent evaporation. As nail lacquer is applied directly to the nail, the film forming composition changes because of loss of volatile composition from the formulation Which is then formed a residual film on surface of the nail. These formulations generally penetrate through the nail by breaking disulfide bond of the nail, then new pores will be formed and better the penetration of drug via nail plate which is beneficial in treating the diseases of nail. Drug release from the film will be governed by Fick's law of diffusion, i.e., the flux (J), across a plane surface of unit area will be given by:

$$J = -D\, dc/dx$$

Where D = diffusion coefficient of the drug in the film

dc/dx = concentration gradient of the drug across the diffusion path of dx the thickness (dx) of the diffusion path grows with time, as the film surface adjacent to the nail surface becomes drug-depleted. Increase in drug concentration in lacquer results in increased drug uptake [6].

2.5 Factors affecting permeation through nail plate

- Molecular size of compound
- Degree of ionization
- Nail plate hydration

- Presence of an intact dorsal layer
- Formulation effects
- Nail thickness and presence of disease
- Nature of vehicle

3. METHODOLOGY

Material: Posaconazole was gifted from DR. Reddy laboratory**,** Hyderabad. Nitrocellulose was obtained from Jyoti Enterprise, Surat Dibutyl phthalate, Ethyl alcohol, Butyl alcohol and Toluene was obtained from Vishal Chem, Mumbai.

3.1 Method

Formulation of nail lacquer: Add solvent (Toluene) and Diluent (Butyl Acetate) and mix well. Then add nitrocellulose while agitating. add resin (santolite) and Plasticizer (Dibutyl phthalate) and remaining of the solvent. and stir till dissolved. At end check the viscosity. then filter it and add colour.

Table-1: Formulation of nail Lacquers of Posaconazole

Ingredients	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Posaconazole	6 %	6%	6%	6%	6%	6%	6%	6%	6%
Nitrocellulose	0.4 gm	0.6 gm	0.8 gm	0.4 gm	0.6 gm	0.8 gm	0.4 gm	0.6 gm	0.8 gm
Santolite	3gm	3gm	3gm	3gm	3gm	3gm	3gm	3gm	3gm
Dibutyl Phthalate	5ml	5ml	5ml	8ml	8ml	8ml	10ml	10ml	10ml
Butyl Acetate	6ml	8ml	9ml	6ml	8ml	9ml	6ml	8ml	9ml
Toluene	7ml	7ml	7ml	9ml	9ml	9ml	11ml	11ml	11ml
Ethyl Alcohol	2ml	2ml	2ml	2.5 ml	2.5 ml	2.5 ml	3ml	3ml	3ml

3.2 Determination of λmax

3.3 Preparation of Standard Stock Solution

In order to confirm λmax of Posaconazole, 100 mg of Posaconazole was weighed accurately and transferred to a 100 ml of volumetric flask. The volume was adjusted to 100 ml with suitable solvent to get a 1000 µg/ml stock solution. From stock solution (1000 µg/ml), 100 µg/ml working solution was prepared by diluting 10 ml of stock solution with 100 ml solvent in volumetric flask. The further stock solution was diluted appropriately, which was then analyzed by UV-visible double beam spectrophotometer between 200 to 400 nm against suitable solvent as blank solution [7].

3.4 Preparation of calibration curve of Posaconazole in Phosphate buffer pH 7.4

From stock solution (1000 µg/ml), 100 µg/ml solution was prepared by diluting 10 ml of stock solution with 100 ml phosphate buffer pH 7.4 in volumetric flask. Accurately measure standard working sample solutions of Posaconazole (1.0, 2.0, 3.0, 4.0 and 5.0 ml) were transferred to a series of 10 ml of volumetric flasks and diluted to obtain the concentration of 10, 20, 30, 40 and 50 µg/ml. The absorption of prepared Posaconazole solution was measured at 225 nm using UV-visible spectrophotometer against Water as blank. The experiment was performed in triplicate and based on average absorbance obtain the equation is generated [8].

3.5 Evaluation of Nail lacquer

3.5.1 Non-volatile content

1gm of sample was taken in a glass Petri dish of about 8 cm in diameter. Sample was spread evenly with the help of tared wire. The dish was placed in the oven at 105^{o}C for1hr the Petri dish was removed, cooled, and weighed. The difference in weight of sample after drying was determined.

3.5.2 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.

3.5.3 Water Resistance

0.2 g of NL was spread on a uniform area of a glass plate and was dried, weighed and placed in a beaker filled with distilled water such that dried lacquer is immersed in it. After 24 hours, the plate was dried with the use of filter paper and was weighed again. Water resistance was obtained as the percentage of loss of weight of lacquer to the actual weight [9].

3.5.4 Drug content

The formulation equivalent to 10 mg of drug was weighed and then transferred to 10 ml volumetric flask containing distilled water. The flask was shaken to dissolve the drug and volume was adjust with distilled water. Absorbance of resulted was measured at wavelength 225 nm in UV- visible spectrophotometer and concentration of drug was calculated.

3.5.5 Diffusion studies across artificial membrane

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 [10].

4. RESULT

4.1 Calibration curve of Posaconazole

Posaconazole shows maximum absorbance at 225 nm in Phosphate Buffer 7.4 respectively and shows linearity in range of 10-50µg/ml.

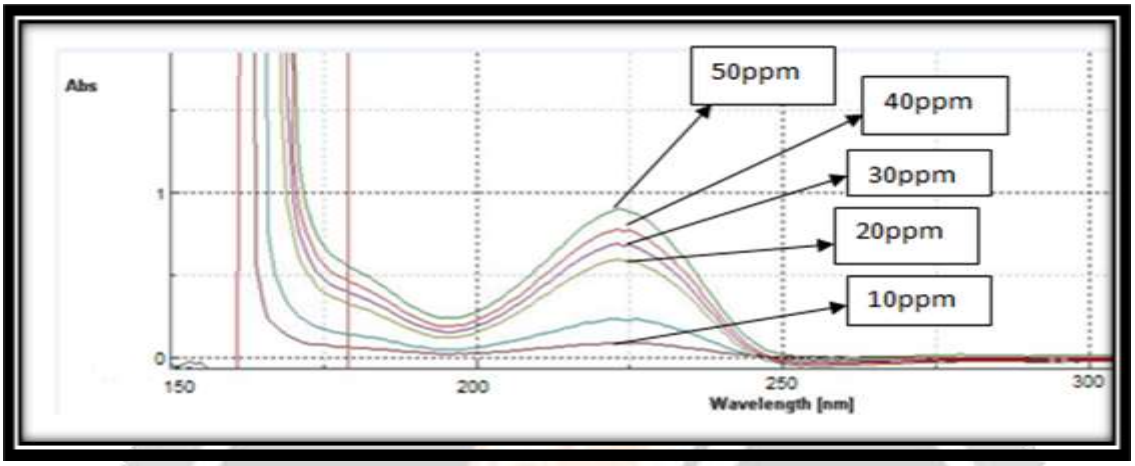

Fig-3: Overlay plot of Posaconazole in PBS 7.4 pH

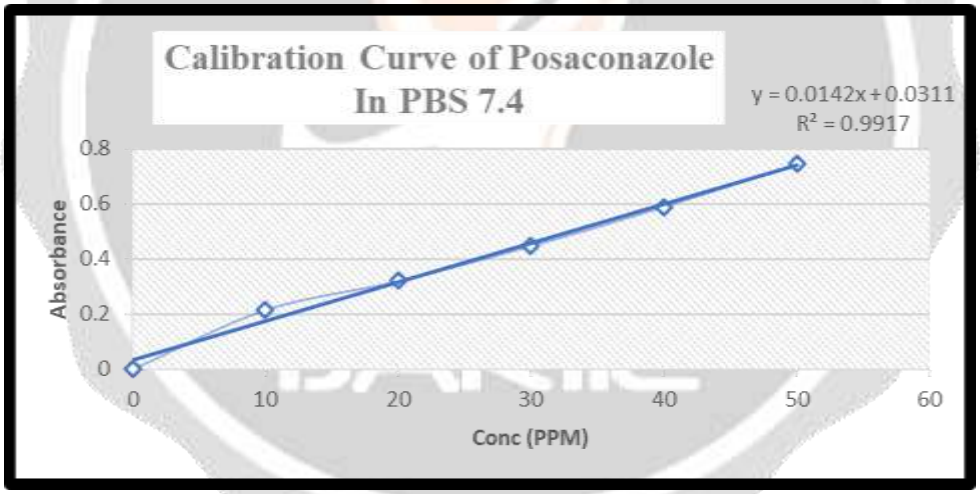

Fig-4: Calibration curve of Posaconazole in PBS 7.4 pH

Table-2: Absorbance at 225nm

SR.NO	Concentration(µg/ml)	Absorbance (mean) (n=3)
1.	0	0
2.	10	0.205
3.	20	0.337
4.	30	0.442
5.	40	0.574
6.	50	0.72

4.2 FT-IR studies

IR spectra of drug were shown as the peaks obtained in the spectra of drug correlates with functional groups of Posaconazole which confirms purity of drug. All the characteristic peaks respective to their functional groups of drugs are shown and comparison of graph done which reveal no interaction with polymer and drug mixture. Figure 5, 6,7 and 8 are shown.

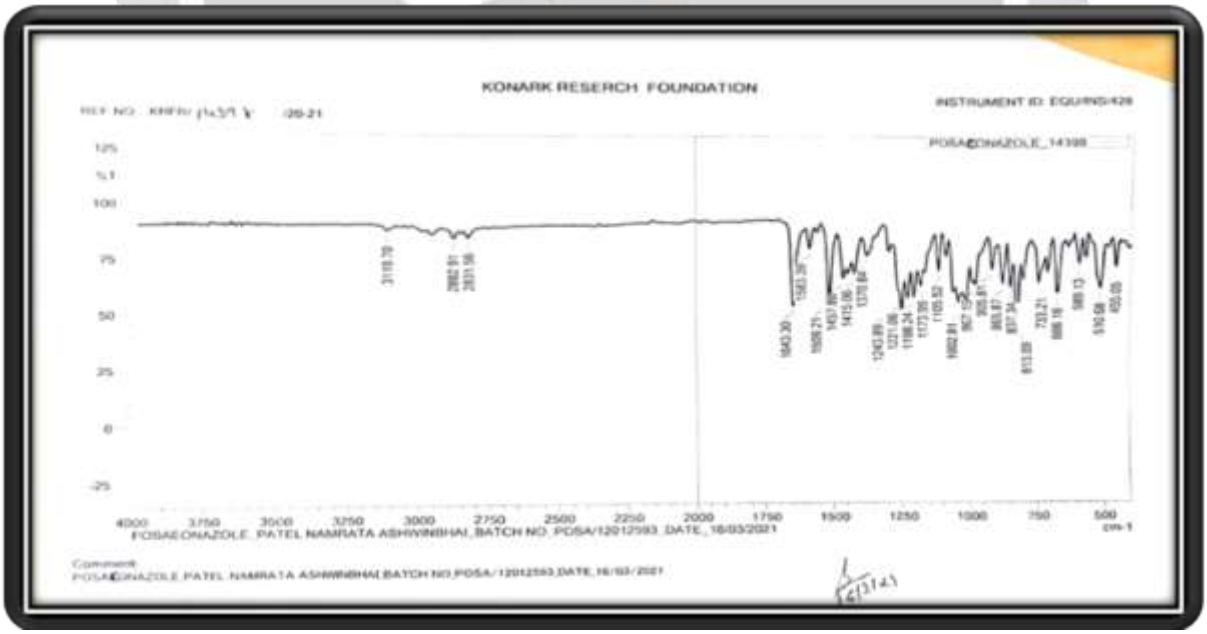

Fig-5: FTIR spectra of Posaconazole

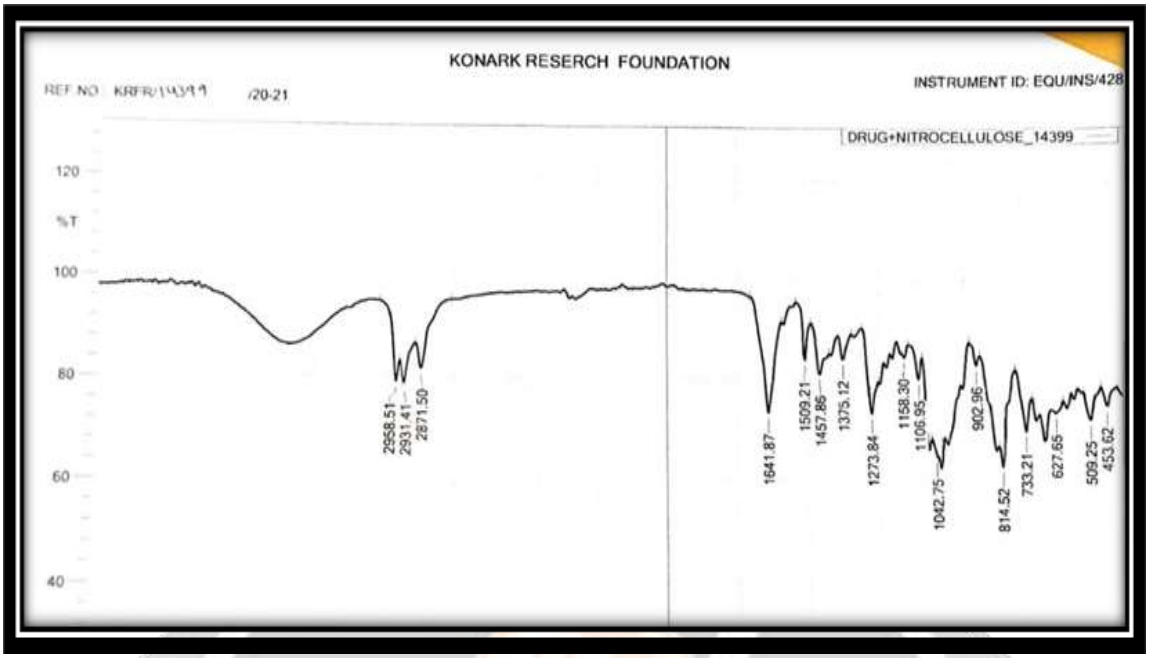

Fig-6: FTIR spectra of Posaconazole + Nitrocelluose

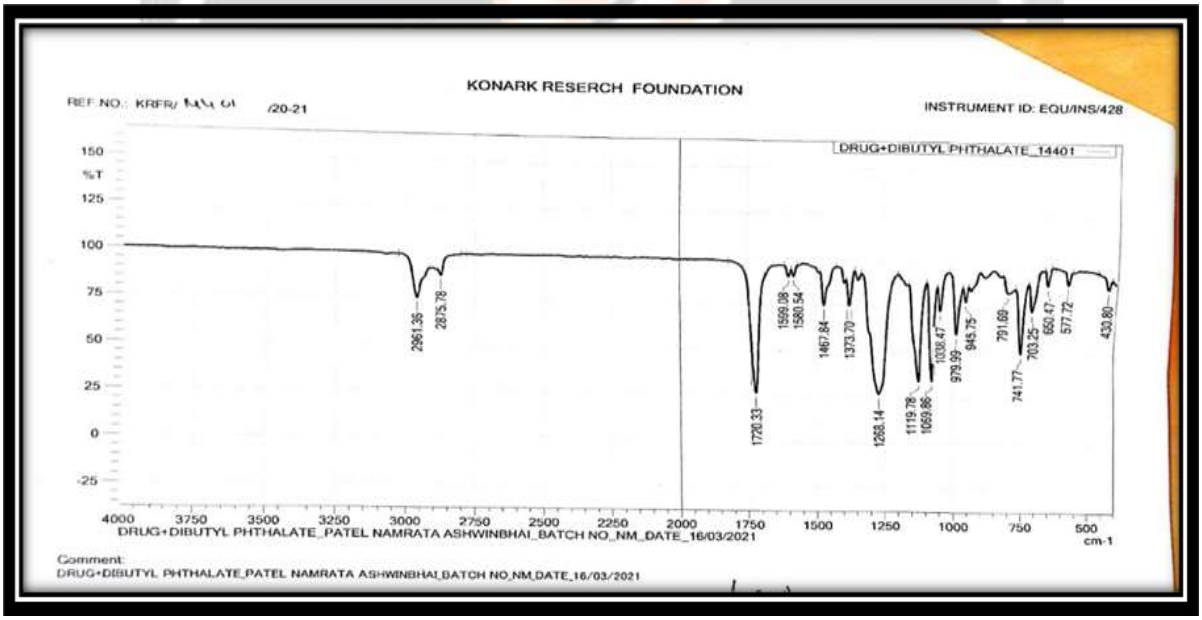

Fig-7: FTIR spectra of Posaconazole + Dibutyl phthalate

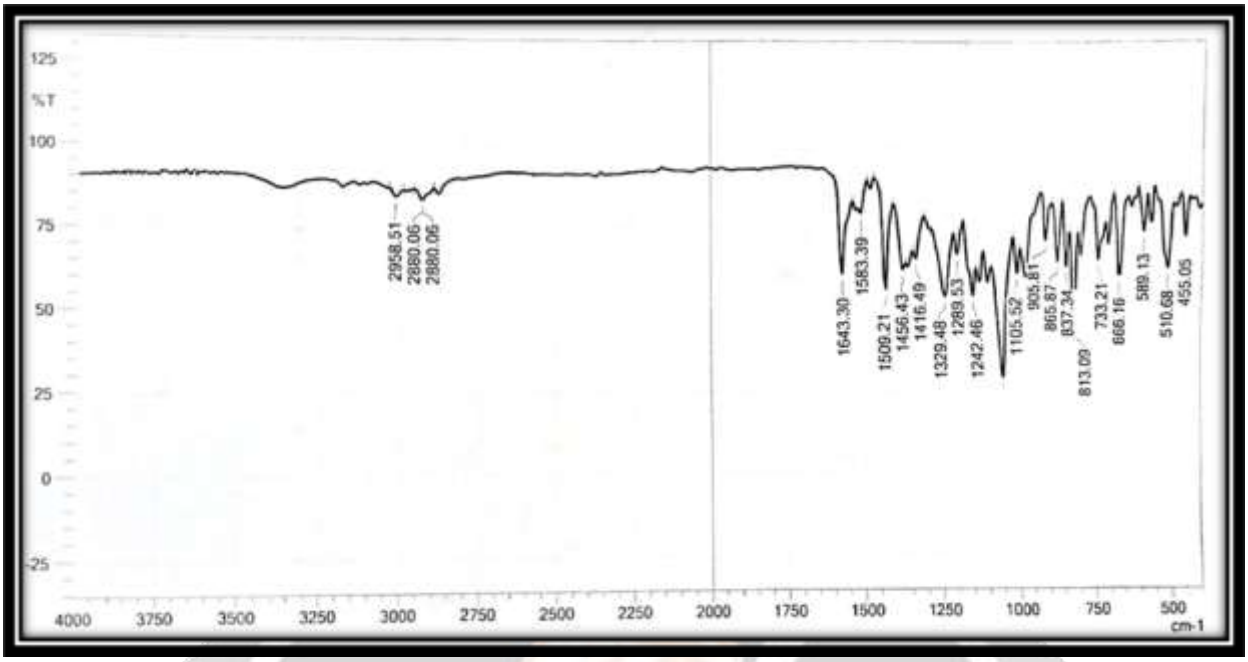

Fig-8: FTIR spectra of Posaconazole with all excipients

4.3 Evaluation Parameter

All the formulation are found to particle free and clear. The pH of the formulation was found to be in the range 4.5-4.8. All these observations are shown in **Table 4**.

4.4 Viscosity

F1 formulation shows lowest range while F9 shows optimum viscosity.

4.5 Drying time

F3 formulation shows less drying time in compared to F8. Optimum result obtained from F8 batch.

4.5 Water Resistance

F3 formulation shows low water resistance while in compared to F9 shows optimum result.

4.6 % Drug Content

The % drug content was found to be in the range of 99.57% to 99.86%.

4.7 % Drug release

The formulation F2 shows drug release up to 66.9% while formulation F9 shows optimum drug release of 87%.

Table -4: Evaluation data of batches

Formulation No	F1	F2	F3	F4	F5	F6	F7	F8	F9
pH	4.6 ± 0.01	4.7 ± 0.02	4.7 ± 0.02	4.6 ± 0.03	4.5 ± 0.06	4.4 ± 0.04	4.6 ± 0.04	4.8 ± 0.01	4.4 ± 0.02
Viscosity (cps)	10.57	11.68	12.04	12.15	12.69	15.04	16.98	17.98	20.66
Drying time (Sec)	64	74	75	66	80	79	67	80	86
Water resistance	0.11	0.21	0.10	0.12	0.22	0.24	0.22	0.12	0.16
%Drug Content	99.57	99.61	99.67	99.75	99.41	99.59	99.66	99.72	99.85

Table-5: Diffusivity study of batches

% CDR									
Time (min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	9.82	11.22	13.35	15.25	26.25	32.12	39.31	29.65	26.52
4	10.20	12.05	14.98	16.88	32.23	43.55	49.85	34.12	31.98
6	13.28	14.35	16.35	17.22	38.51	52.82	59.65	45.56	40.43
8	16.42	17.88	18.85	20.13	46.52	61.65	67.72	51.16	44.19
10	26.58	28.95	32.05	30.35	48.22	69.35	76.45	62.34	53.22

12	32.45	36.33	40.20	36.15	56.23	76.25	85.05	69.74	60.13
16	43.10	42.30	48.38	42.95	65.15	80.02	92.15	75.93	68.66
20	48.22	49.98	51.80	50.10	77.45	83.35	98.40	81.45	72.32
24	49.65	50.80	52.61	54.32	79.92	88.95	96.25	93.23	83.45
28	52.55	54.89	56.80	58.38	82.40	89.00	98.23	96.81	89.76
32	56.25	58.75	59.33	60.21	80.25	86.32	93.15	95.00	95.84
36	58.95	59.98	61.28	63.45	79.45	84.15	91.82	94.57	93.78
40	60.18	62.15	66.92	66.21	77.31	82.15	90.08	93.14	90.72
44	62.52	63.25	65.99	68.84	76.65	80.85	89.16	90.76	89.87
48	65.82	66.9	68.34	69.1	73.51	77.09	84.36	87.2	87.0

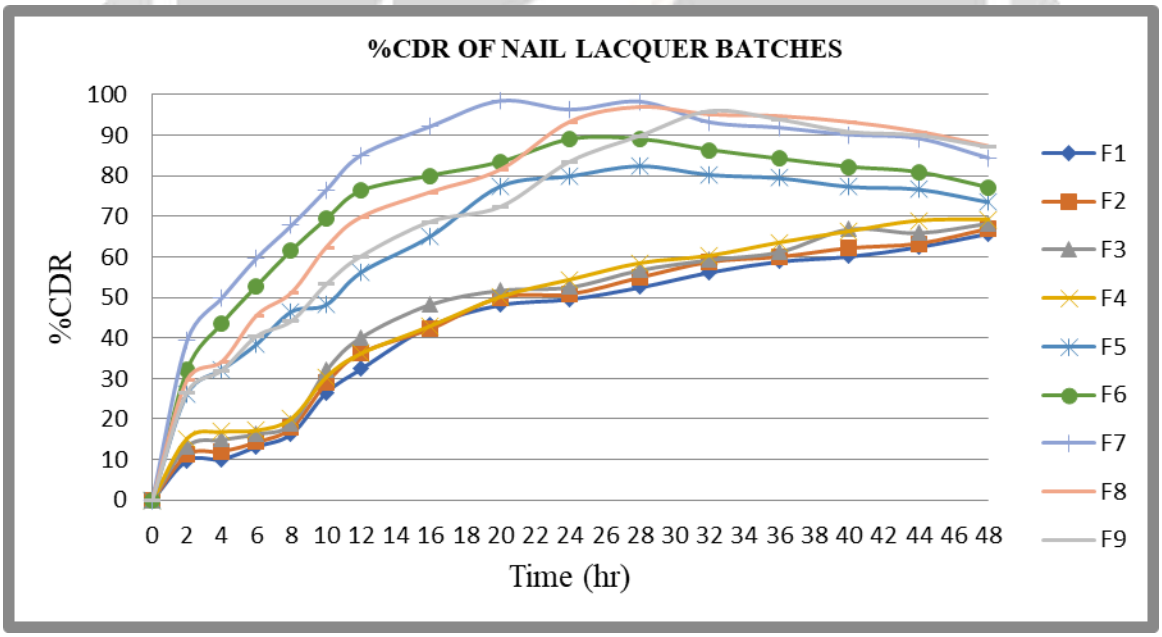

Fig-9: % CDR of Nail lacquer batch

5. CONCLUSION

Nail Lacquer of Posaconazole was successfully formulated by using Homogenization method and was developed to a satisfactory result, in terms of pH, viscosity, drying time, water resistance, % drug content. All formulation

was found to be particle free and clear. Formulation F9 with 0.6gm of nitrocellulose and 8ml of dibutyl phthalate shows drying time, water resistance, viscosity and % drug content for extended time. Formulation F9 also shows the highest % drug content of 99.85 % along with the drug release of 87.0%.

6. REFERENCE

[1]. Philip R. Cohen, MD, "Onychomycosis diagnosis", *Indian J Dermatol Venereol Leprol.* **2012**; 78:263-270.

[2]. Cohen PR, Scher RK, "Topical and surgical treatment of onychomycosis", *J Am Acad Dermatol*.**1994**, 31: S74-S7.

[3]. Shirwaikar A, Thomas T, Lobo R, "Treatment of onychomycosis. An update", *Indian J Pharm Sci.* 2008 Nov-Dec;70(6):710-714.

[4]. Kanchan Yadav, "Antifungal Nail Lacquer using treatment of onychomycosis", *International Journal of Scientific and Research Publications*, Volume 9, Issue4. April **2019.**

[5]. Apeksha R Rathi, Ritesh R Popat, "Nail drug delivery system", *International Journal of Pharmaceutical Chemistry and Analysis*, January- March, **2020**:7(1):9-21.

[6]. Patel RP, Naik SA, Patel NA, "Drug delivery across human nail", *International Journal Current Pharm Res*, Volume I, Issue 2009, 01:01-7.

[7]. Dr. Jai Narayan Mishra, Mr. D.K Vishwakarma**, "**Formulation and Development of Antifungal Nail **l**acquer containing miconazole nitrate use in treatment of onychomycosis", *International Journal of Scientific and Research Publications*, Volume 9, Issue 4, April **2019.**

[8]. Arun Raj, Nithin Kurian**, "**Formulation and Evaluation of Transungual Drug Delivery of Fluconazole using permeation enhancers screened by hydration of nail plate", *Research & Reviews: A Journal of Pharmaceutical Science*. **2016;** 8(3): 32-45.

[9]. Kiran SR, Chandrashekhar B, Vishnu P, "Ungual drug delivery system of ketoconazole nail lacquer", *International Journal Applied Pharm.* **2010**; 4:17-19.

[10]. Sabreen J, Divyakumar B, "Preungual drug delivery systems of terbinafine hydrochloride nail lacquer", *Asian Journal Pharm*. **2008**; 02:53-66.