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FORMULATION & EVALUATION OF MEDICATED NAIL LACQUER OF FLUCONAZOLE

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ABSTRACT

Topical therapy is desirable in treatment of nail diseases like Onychomycosis (fungal infection of nail) and psoriasis. The purpose of this study is to explore the difficulties in penetration of drug across nail plate & enhancement of bioavailability of antifungal drug. Many formulations of fluconazole were prepared namely F1, F2, F3 and F4 and evaluated for various processing parameters including *in-vitro* release (Diffusion) studies in 7.4 pH phosphate buffers. Effect of varying concentration of various excipients were studied after evaluated non-volatile content Drying time, film forming & diffusion rate, drug content analysis, antifungal activity, kinetics release studies. In drug excipients compatibility studies there was no chemical incompatibility between the drug and polymer. In *in-vitro* diffusion studies and *in-vitro* permeation studies it was found that formulation F3 showed better diffusion and permeation. On the basis of current investigation, this system may improve patient's compliance.

KEYWORDS: Nail Lacquer, Fluconazole, Ethyl cellulose, Toluene, Castor oil, Glycerin, Thioglycolic acid, Acetone.

INTRODUCTION

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders or the cutaneous manifestations of a general disease (e.g. Psoriasis).[1]

"Trans" means "through" and "Unguis" means "Nail", so transungual drug delivery system is nothing but a system related with drug delivery through the nail to achieve a targeted drug delivery system of the nail to treat diseases of nail itself. The nail plate may show nonstandard as a result of decreased glow. It`s participation of nail bed, decrease of blood supply, physical or chemical skin texture of nail bed. The ventral layer consists of stretchy hyponychial in which many pathological changes occur. As a result, in the action of these nail diseases; an effective drug concentration in the ventral nail plate would be of great significance.

Common diseases of nail

The nail plate may appear abnormal as result of, a disease of skin of the nail bed, troubles in blood supply, trauma, tumors of the nail fold and nail bed, infectivity of the nail fold, infection of the nail plate.

- Onychomycosis
- Onychatrophia
- Onychogryposis
- Onychorrhexis Onychauxis
- Leuconychia
- Koilonychia

Necessary of the treatment

Although nail disorders are living threatening, they may be painful, discomfort and disfiguring for the victim and may produce serious physical and occupational limitations, psychological and moving effects, and affect class of life (QOL). distorted nails can lead to surrounding tissue harm and once again may promote secondary bacterial infection.[2]

Treatment available for Onychomycosis

Identified methods of treatment fall into three categories:

1. Removal of all or division of the affected nails
2. Oral/systemic therapy
3. Topical/Ungual therapy

Nail lacquers

Medicated nail lacquers are the formulations that are used for transungual drug release system for maximal antifungal effectiveness. After application, the solvent as of the lacquer formulation evaporates leaving an occlusive film on which the drug concentration is add to than in the unique formulation.

METHODS OF PREPRATION

Preparation of Standard solution

Accurately weighted 100 mg of Fluconazole were separately taken into 100 ml volumetric flasks and dissolved in small quantity of 7.4 pH phosphate buffer, the volume were made up with the buffer solution, to obtain a solution containing 1mg/ml.[3]

Preparation of Stock solution

From the standard solution, a stock solution was prepared by pipette out 1 ml of above standard solution in to another 100 ml volumetric flasks and volume was made with the 7.4 pH phosphate buffer solution, to give a solution containing 100 µg/ml.

Preparation of working standard solution

Aliquots of 2, 4, 6, 8, and 10 ml of stock solution were pipette out into 10 ml volumetric flasks. The volume was made up to the mark with 7.4 pH phosphate buffer. These dilutions give 2, 4, 6, 8 and 10 µg/ml concentration of Fluconazole. The absorbance of prepared solution of Fluconazole in was measured at 261 nm in Shimadzu UV-1800 spectrophotometer against an appropriate blank (7.4 pH buffer).

Preparation of fluconazole nail lacquer

Fluconazole nail lacquer was prepared by simple mixing method. Where in the formulation concentration was kept constant. The amount of ethyl cellulose, toluene, castor oil, Glycerin were mixed till it gives the uniform distribution of the component which is used in the nail Lacquer. Now the fluconazole if also mixed in the solution and kept on the magnetic stirrer till fluconazole is mixed properly and then the thioglycolic acid added and mix the solution on magnetic stirrer then till the Solvent mixed and volume made up to fix quantity and mixed properly. (Table1).

EVALUATION PARAMETERS

PREFORMULATION STUDIES OF FLUCONAZOLE

Spectrum measurement

The standard solution of Fluconazole was prepared by dissolving 100mg in 100ml of phosphate buffer pH 7.4, extra diluted to get 100µg and was scanned between 400-200nm in UV-Visible spectrophotometer to obtained ƛ max.

Construction of calibration curve

Preparation of 7.4 pH phosphate buffer solution

Placed 1.19 gm of disodium hydrogen phosphate in 500-ml volumetric flask, add the 0.8 gm of potassium dihydrogen phosphate add 4 gm sodium chloride and make volume up to 500 ml level spot with the help of Distilled water.

Preparation of standard calibration curve

Fluconazole exhibited peak absorbance at 261 nm in 7.4 pH phosphate buffer.

Instrument used

ELICO UV SL-210, Double beam UV spectrophotometer.

DRUG EXCIPIENTS COMPATIBILITY STUDIES

FTIR could be used to investigate and predict any physiochemical interaction between different excipients.[4]

EVALUATION STUDIES FOR PREPARED NAIL LACQUER

Non Volatile Content

Taken 4 Petridis. Mark then as F1, F2, F3, F4. Sample was taken in glass Petri plate of about 8 cm in dia. Sample was spread uniformly. Then weigh individually to the F1, F2, F3, and F4. The Petri plate is put in the hot air oven under 105ºc for 1 hr. After 1 hr it is removed, cooled and then weight.[5]

Drug Content estimation

Nail lacquer equivalent to 200 mg was dissolved in 50 ml phosphate buffer solution of pH 7.4. Then the solution was ultrasonicated 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 261 nm and determined the drug content.

In- vitro transungual permeation studies

In vitro transport studies were carried out using Franz diffusion cells respective volume 25 ml, were performed by using Franz diffusion cell at 37 ± 5°C and phosphate buffer (pH 7.4) fitted with a custom made Teflon nail holder. Drug solution equivalent to 100 µg prepared in buffer was placed in the donor compartment. The receiver compartment was filled with phosphate buffer (pH 7.4) volume was 25 ml. The active diffusion area was 0.25 cm^2. The receiver compartment was stirred at 600 rpm with a 3-mm magnetic stir bar. Intermittent samples of 2 ml were drawn from the receiver compartment at 2 h intervals for 36 h and the amount of fluconazole transported was measured. Equal volume of fresh buffer was replaced in the receiver compartment followed by each sampling. The drug analysis was by using double-beam UV spectrophotometer, at 261 nm.[7]

Determination of zone of inhibition

Antifungal activity was checked by cup plate method. In this method a previously liquefied molten sabouraud dextrose agar media was inoculated with 0.2 ml of fungal suspension of Candida albican (received as a gift sample from shreya life sciences, Roorkee) having a uniform turbidity at temperature of 4 to 8°C. 20 ml of culture medium was poured into the sterile Petridis having an internal of 8.5 cm. Care was taken for the uniform thickness of the layer of medium in different plates. After complete solidification of liquefied inoculated medium, the wells were made aseptically with cork borer

having 6mm diameter. In one plate formulation (nail lacquer) and in another plate pure drug solution was placed carefully. Plates were kept for pre diffusion for 30 min. After it normalized to room temperature; the plates were incubated at 22- 27°C for 72hrs. After incubation period was over, the zone of inhibition was measured with help of scale.[8]

RESULT AND DISCUSSION

Spectrum Measurement

In spectra measurement of fluconazole ƛmax was found to be 261 nm using phosphate buffer pH7.4. In spectra measurement of Fluconazole λ max was found to be 261 nm (fig.1).

Construction of Calibration Curve

The calibration curve of fluconazole was obtained in range of 10-100µg/ml at the wavelength of 261nm using phosphate buffer pH 7.4 as medium with a regression coefficient of 0.991 (r^2 value) (fig.2).

Drug Excipients Compatibility Studies

All the characteristic IR peaks related to pure drug, fluconazole also appeared in IR spectrum of mixture of fluconazole with ethyl cellulose. (fig. 3 & fig. 4).

Non Volatile Content

Non-volatile content result for formulation F1 and F2 is given in table, it was seen that as the polymer concentration increases the non-volatile content increases. Non- volatile content depends and varies upon the concentration of polymer used.

Water Resistance

In water resistance test, it can be seen as the polymer concentration increases the water resistance increases, as the concentration of polymer decreases the water resistance decreases. Lower the increase in the weight of the nail lacquer film higher is the water resistance capacity. (Table).

Drug Content estimation

Result of content uniformity test was determined. These result showed that the method of preparation of nail lacquer gave reproducible result. The drug content for formulation F1 to F4 was found to be in range of 99-90%.

In -vitro Transungual permeation studies

In-Vitro diffusion studies were conducted using diffusing cell for 36 hours. formulation F2, F4 containing highest concentration of penetration enhancer (Thioglycolic acid) showed the highest release of 93.41% and 97.52%. it found that as the penetration enhancer concentration increases the release of drug increases. From the data obtained by evaluation of nail lacquer, formulation F3 was found to be best formulation among all the four formulations (fig.5).[9]

Determination of zone of inhibition

The zone of inhibition for pure drug was found to be 23mm and for best formulation 20-23mm (Table 7). it was found that best formulation F3 was effective as pure drug as the zone of inhibition of best formulation.[10]

Table 1: Formulation composition for fluconazole nail Lacquer.

Formulation	Drug (mg)	Ethyl cellulose (gm)	Toluene (ml)	Thioglycolic acid (ml)	Glycerin (ml)	Castor oil (ml)	Acetone (ml)
F1	20	2	2.6	0.2	2	3	20
F2	20	2	2.6	0.5	2	3	20
F3	20	3	2.6	0.2	2	3	20
F4	20	3	2.6	0.5	2	3	20

Table 2: Non volatile content of fluconazole nail Lacquer.

Formulation	Weight of empty petri dish	Weight of petri dish with layer	Weight of petri dish after drying	Difference
F1	42.48	45.65	44.64	1.01
F2	42.48	45.21	43.64	1.57
F3	42.48	44.51	43.54	0.97
F4	42.48	44.94	43.72	1.42

Table 3: Drug content estimation.

S.No	Formulations	% Drug Content ± SD
1.	F1	94.32±0.209
2.	F2	96.77±0.478
3.	F3	98.43±0.065
4.	F3	97.36±0.167

Table 4: *In -vitro* transungual permeation studies (percentage Drug Release from Various Formulations of Fluconazole).

Formulations	Time(hr)											
	2	4	6	8	10	12	16	20	24	28	32	36
F1	22.53	28.61	34.5	42.9	47.36	51.23	55.69	62.20	66.21	74.23	84.10	90.52
F2	21.73	25.34	32.15	39.27	44.03	49.8	54.39	60.3	64.57	72.00	83.72	93.41
F3	24.66	29.89	35.66	44.66	49.31	53.81	57.36	63.58	69.09	75.05	86.09	97.52
F4	21.45	28.86	33.62	42.54	47.04	52.05	54.04	62.05	65.6	74.94	82.76	84.04

Table 5: For zone inhibition activity.

S.No	Area of Pure Drug in (mm)	Area of Formulation in(mm)
1	23mm	20.9
2	23mm	21.6
3	23mm	22.6
4	23mm	22.1

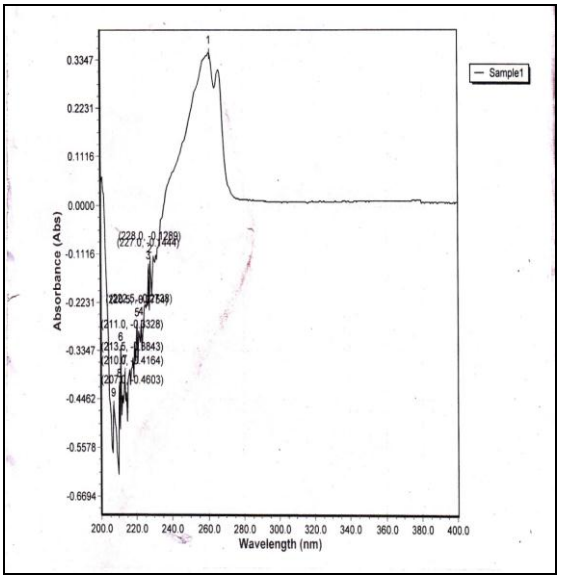

Fig. 1: UV Spectrum of Fluconazole.

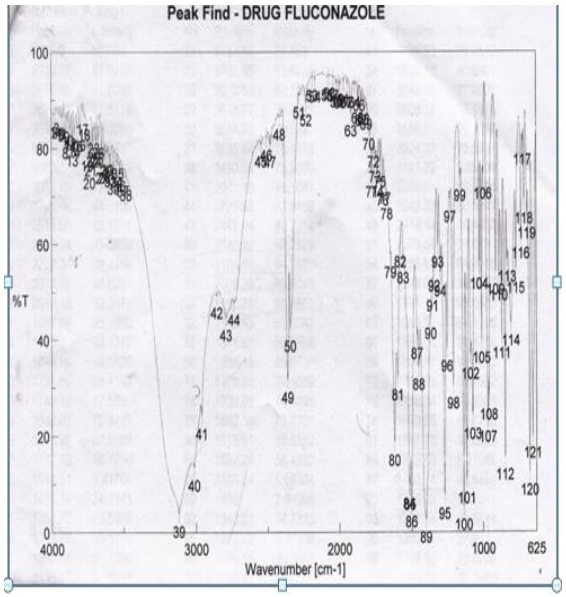

Fig. 3: FTIR Spectra of Fluconazole (drug).

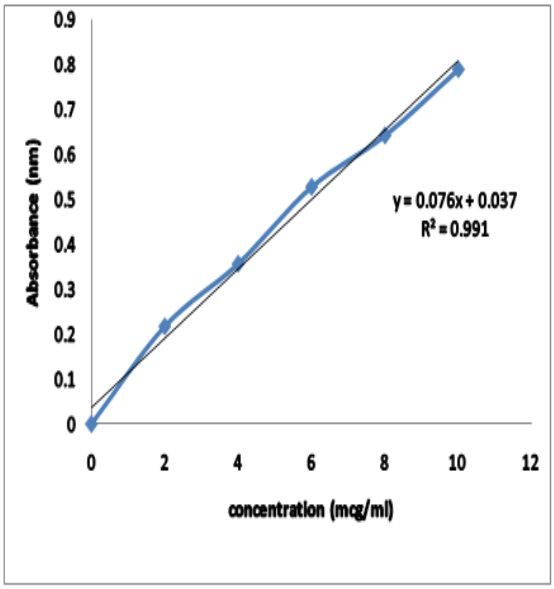

Fig.2: Calibration curve of Fluconazole in 7.4 pH phosphate buffer at 261 nm.

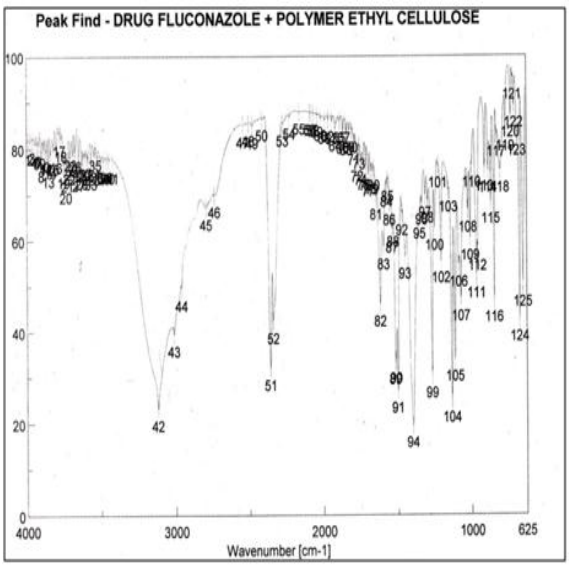

Fig. 4: FTIR Spectra of Fluconazole + Ethyl cellulose (drug + Polymer).

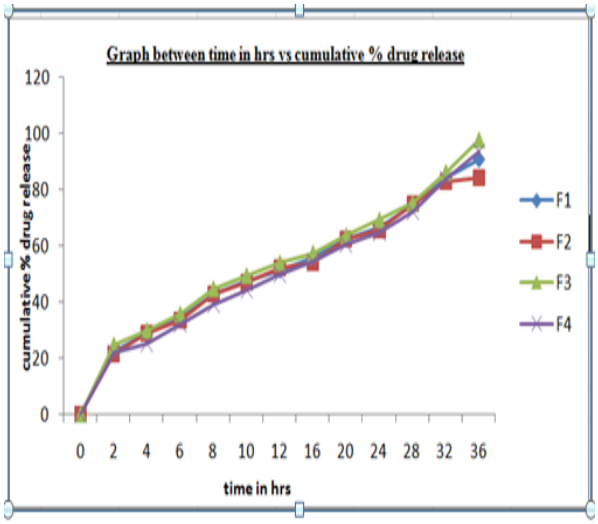

Fig. 5: *In-Vitro* Drug Release profiles of various formulations at pH 7.4 phosphate buffer.

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