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FORMULATION AND EVALUATION OF MEDICATED NAIL PATCHES CONTAINING KETOCONAZOLE

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ABSTRACT

The present investigation aims to formulate and evaluate a medicated nail patch for the treatment of diseases like Onychomycosis (fungal infection of nail) and psoriasis, Yellow nail syndrome, Paronychia and many others. The objective of this is study to explore the difficulties in penetration of drug across nail plate & to enhance bioavailability of antifungal drugs. Nail drug delivery system is used to reduce such a hazardous systemic effects and provides longer contact time at a site of action. Many formulation of Ketoconazole were prepared by using optimized formula using HPMC100, Eudragit RS100, DCM : methanol, diethyl phthalate, propylene glycol which shows better diffusion & permeation. These are evaluated for various parameters including thickness, folding endurance, weight variation, % moisture uptake, and % moisture loss and in-vitro release (Diffusion) studies in 7.4 pH phosphate buffers. Effects of varying concentration of various polymer and penetration enhancer were studied. The evaluation of that patches is carried out by drug excipient interactions subjecting to FTIR Spectral analysis, in-vitro diffusion studies, drug content analysis, NDDS is used to achieve maximum therapeutic effect along with improve patient's compliance.

KEYWORDS: *Ketokonazol, HPMC100, Propylene Glycol, Nail Patches, In-Vitro Release*

INTRODUCTION

The transungual drug delivery system in this system Trans means through and unguis means nail. Nail plate is responsible for penetration drug across it. Hence transungual drug delivery system is a system associated with drug delivery across nail barrier to achieve a targeted drug delivery to treat fungal nail diseases. Two main diseases affect the nail unit one is onychomycosis and second one is psoriasis. Treatment of these two diseases usually leads to poor patient compliance. Nail fungal infection treatment are difficult to treat effectively because of insufficient concentration reach to the site of action. The main advantages of nail patches i.e., Patient will not feel like as medication, easily removed when needed and Improved patient compliance. There are variety of topical formulations like gels, creams and also ointments which are commonly used for the treatment of nail infections but affect in the treatment is limited because of their relatively low impermeability. Transungual topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery, and also provides controlled release of the drug for extended period of the time.

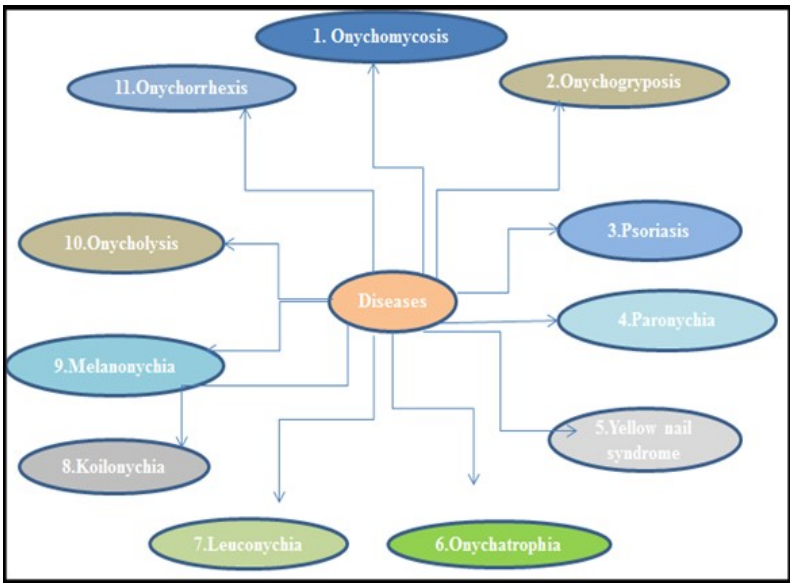

Figure 1: Diseases Affecting the Nails.

ONYCHOMYCOSIS

Yellow-brown patches near the lateral border of the nail. Beneath the masses of soft horny debris accumulate & the nail plate gradually becomes thickened, broken & irregularly distorted. And secondary effects include irritation, pain and pressure. The incidence of Onychomycosis has been increasing and is related to diabetes, a suppressed immune system, and signs with aging. One or many nails may be affected & there may be associated infection of the skin. It is a fungal disease caused by three classes of organism:

- Dermatophytes
- Yeast
- Non Dermatophyte Molds

Dermatophytes

Trichophytonrubrum is the most common dermatophyte involved in Onychomycosis. Other dermatophytes that may be involved are Trichophytoninterdigitale, Epidermophytonfloccossum, Trichophytonviolaceum.

Other Pathogens

Other causative pathogens include Candida and non dermatophytic molds, in particular members of the mold generation Scytalidium (name recently changed to Neoscytalidium), Scopulariopsis. Candida mainly causes fingernail onychomycosis in people whose hands are often submerged in water. Scytalidium mainly effects people in the tropics, though it persists if they later move to areas of temperate climate.

Clinical Types of Onychomycosis

There are seven subtype clinical patterns of Onychomycosis:

- DLSO – distal and lateral subungual Onychomycosis
- SO – superficial Onychomycosis (white or black)
- EO – end onyx onychomycosis
- PSO – proximal subungual onychomycosis
- MPO – mixed pattern Onychomycosis
- TDO – total dystrophic onychomycosis
- Secondary onychomycosis- another subtype represents the end stage of the progression of all the above subtypes.

OBJECTIVE

In this present work, we are planning to prepare Nail patches of the following objective.

- To selection drug and excipients for the preparation of medicated nail patches.
- To determine compatibility study.
- To prepare nail patches using polymers of varying concentration by solvent casting technique.
- The prepared Nail patches will be evaluated for various parameters like weight variation, thickness, flatness, folding endurance, drug content, percentage of moisture content, etc.
- To study the in vitro drug diffusion.
- To carry out the stability study as per ICH guidelines.
- To overcome degradation, gastric irritation and the first pass metabolism of drug.
- To improve the therapeutic efficacy of drug.
- Avoidance of hepatic metabolism because the drug from the Nail patch is directly entering in to the systemic circulation.

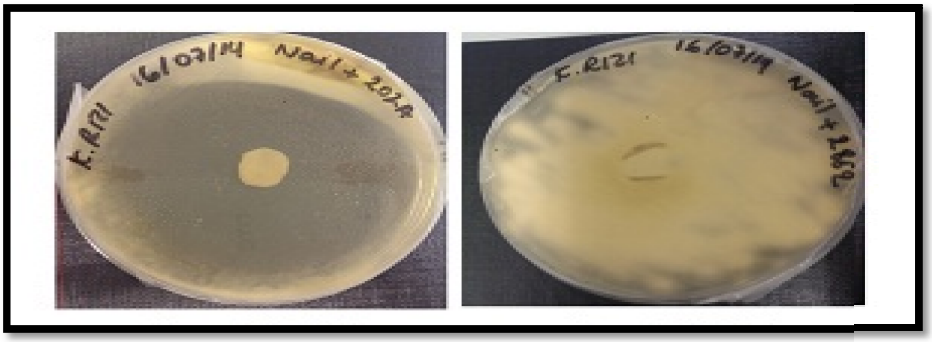

Figure 2: Medicated Nail Patches.

Ketokonazol is an antifungal infection used to treat no of fungal infections, applied to fungal skin infection such as tinea, cutaneous candidiasis, dandruff, dermatitis .Oral bioavailability of ketokonazol is 37-97 % and the elimination half life is biphasic.

HPMCK100 also known as hypromellose. It provides the release of drug in a controlled manner. Effectively increasing the duration of release of drug to prolong its therapeutic effect, and have high water absorptive capacity. it acts as an excellent hydrophilic gel forming polymer.

Eudragit RS100 is a film forming polymer which is freely soluble in mixture of organic solvent. These polymer formed clear. Low viscosity. Homogeneous film was produced by controlling polymer and plasticizer concentration in nail patches .DMC: Methanol is used an equal ratio as organic solvent .

Propylene glycol is used as an plasticizer, solvent and preservatives.

Diethyl phthalate is a colourless liquid with a slight aromatic odour and low volatility. Diethyl phthalate is used as a plasticizer.

MATERIALS AND METHODS

Materials

Ketoconazole was received a gift sample from Aarti Pharmaceutical Ltd., Pune., Hydroxyl propyl methyl cellulose (HPMCK100) and Eudragit RS 100 were obtained from Loba Chemicals Pvt. Ltd., Mumbai. All other chemicals and solvents were of analytical reagent grade.

Methods

Preparations of Medicated Nail Patch:

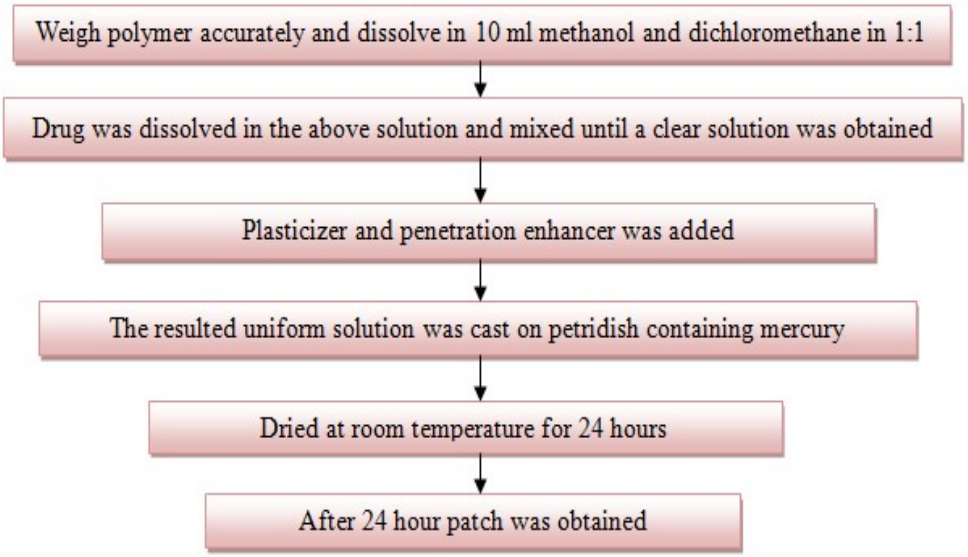

Table 1: Composition of Medicated Nail Patches

Batch Code	F1	F2	F3	F4	F5	F6
Ketoconazole (mg)	200	200	200	200	200	200
HPMC K 100 (mg)	250	275	300	325	350	375
Eudragit RS 100(mg)	250	225	200	175	150	125
Total Weight of Polymer(mg)	500	500	500	500	500	500
DCM:Methanol (1:1)(ml)	10	**10**	10	10	10	10
Diethyl Phthalate (ml)	1	1	1	1	1	1
Propylene Glycol (ml)	1	1	1	1	1	1

PREFORMULATION STUDY

Physical Characteristics of Drug

The physical identification of ketokonazole was done by checking its physical appearance i.e. colour, odour and taste. Weighed quantity of ketokonazole as drug was taken and viewed in well illuminated place. Very less quantity of drug was smelled to get the odour.

Determination of Melting Point

Melting point of the drug was determined by using capillary method. Drug was filled into capillary tube by sealing its one end at the height of 3mm from the closed end. The capillary was introduced into the digital melting point apparatus and the point at which the drug starts melting was noted until the entire samples get melted.

Determination of Partition Coefficient

Partition coefficient was determined by taking excess amount of ketokonazole in 10 ml mixture of n-octanol and water (1:1) in a separating funnel. The system was shaken intermittently for 30 mins and kept undisturbed for overnight to achieve equilibrium. Then the two phases were separated and centrifuse at 10000 rpm for 15 minutes. After centrifugation, the concentration of ketokonazole in both phases was determined by measuring the absorbance at 244 nm on UV- visible spectrophotometry. The partition coefficient determined by formula :

P (O/W) = C1(oil)/C2(water)

Where, C1 (oil) =conc. of solute in organic phase.

C2 (water) = conc .of solute in aqueous phase.

P (O/W) = partition coefficient.

Log P = log (O/W)

ANALYTICAL METHODS

Standard Solution

10 mg of ketokonazole was dissolved in 10 ml of methanol to give the concentration of 1 mg/ml (1000ug/ml)

Preparation of Ketokonazole Stock Solution in Methanol

From the above standard solution (1000g/ml) is pipette out and diluted up to 10 ml which gives 100ug/ml. from this solution 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 ml, 1.2 ml, pipette out in a 10 ml volumetric flask and finally diluted up to the mark which gives required concentration that is 2ug/ml, 4ug/ml, 6ug/ml, 8ug/ml, 10ug/ml, and 12ug/ml.

DETERMINATION OF ANALYTICAL WAVELENGTH

Preparation of Standard Calibration Curve of Ketokonazole in Methanol

10 mg of drug (ketokonazole) was accurately weighed from calibrated digital weighing balance and was transferred to 100ml volumetric flask. Small quantity of methanol was added to dissolved the drug. The volume was made up to 100 ml using methanol to prepare stock solution of 100ug/ml. from the stock solution 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 ml of solution was pipette into 10ml volumetric flasks and volume was made up to 10 ml to from concentrations of 2, 6,4, 6, 8, 10, and 12 ug/ml with methanol. The absorbance was measured with the help of UV Spectrophotometer at 244nm by taking methanol aqs reference solution.

FTIR Study of Drug

Infrared spectrum is the technique based upon the simple fact that the substance shows marked selective absorption in the infrared region. After absorption of IR radiation, the molecule of the chemical substance vibrate at many rates of vibration, giving rise to close-packed absorption bands, called as IR spectrum which extend over a wide wavelength range. IR spectrum shows various bands which will correspond to the characteristics functional groups and bands present in the chemical substance. This help to establish the structure of unknown compound as well as analysis of functional group. The sample of drug was analyzed between 4000-600 $^{cm-1}$.

Drug-Excipient Compatibility Studies

The studies were carried out using IR method with the help of Perkin Elmer 1615 spectrophotometer

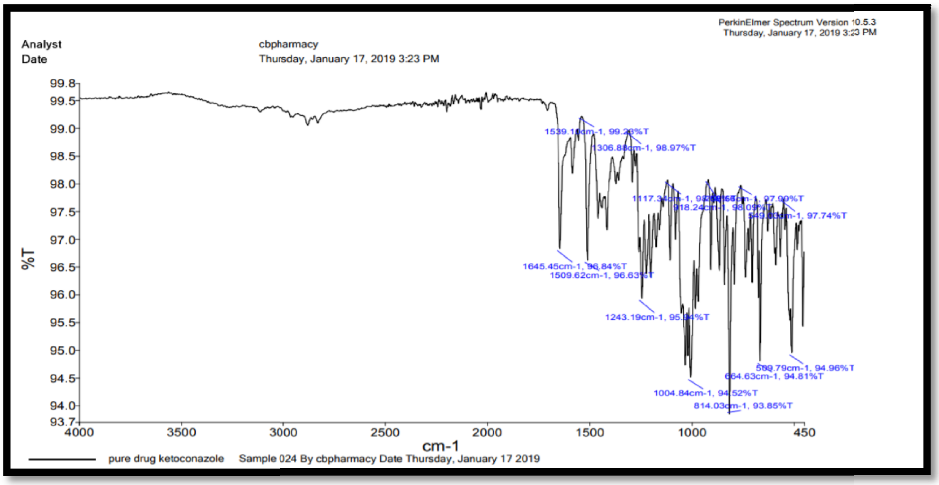

Figure 3: FTIR Study of Ketoconazole.

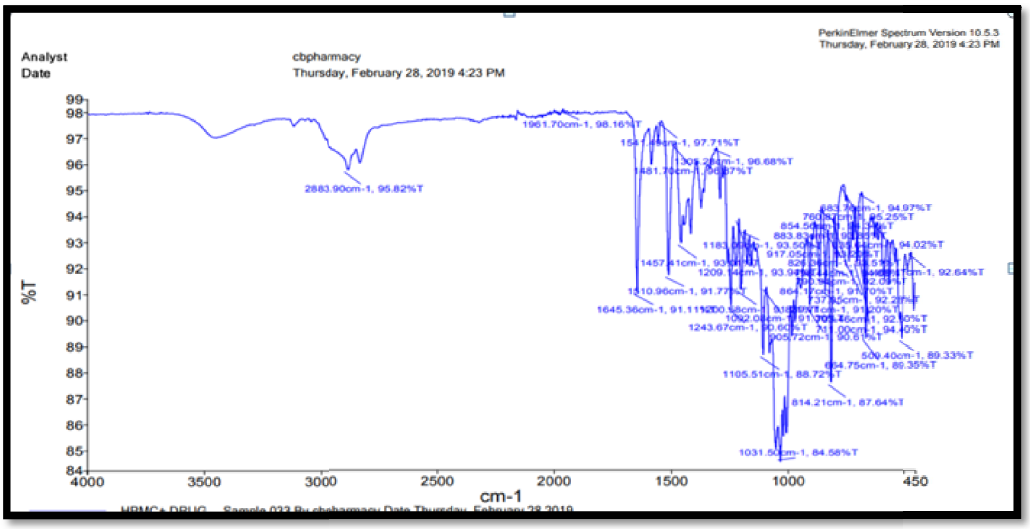

Figure 4: FTIR Study of Formulation.

Physicochemical Characteristics of Medicated Nail Patch

- **Thickness:** The thickness of patch was measured by using vernier calipers, with a least count of 0.01 mm. The thickness uniformly was measured at three different sites and average of three reading was taken with standard deviation.
- **Uniformity of Weight:** Weight variation is studied by calculating the average weight of randomly selected individually weighed patches. The individual weight that evaluated from weight variation test should not be deviated significantly from average weight.
- **Drug Content:** Weigh accurately portion of patch (equivalent to 100mg of drug) and dissolved in 100ml of phosphate buffer solution (7.4 pH) in a 100ml volumetric flask. Place the flask on the shaker for 24hrs. To achieve the complete dissolution. Then they obtained solution was filtered and the content was estimated spectrophotometrically at 244nm by appropriate dilution.
- **Folding Endurance:** The folding endurance test of formulated patches was performed manually by folding the patch repeatedly at the same place (single point) till it broken. The no of times that the patch subjected to repeated folding at the same place without cracking/breaking indicates the folding endurance value. Folding endurance evaluation test involves the determination of folding capacity of the film that subjected to folding at the frequent extreme conditions which also an indicative of brittleness.
- **Percentage Moisture Uptake:** Accurately weighed patches were placed in desiccators containing 100ml of saturated solution of potassium chloride, which maintains at 80-90% RH. After 3 days, the desiccated patch were taken out and subjected to weighing. The % moisture absorption was calculated using the formula:

$$\% \text{ moisture uptake} = \frac{\text{final wt- initial wt}}{\text{initial wt}} * 100$$

- **Percentage Moisture Loss:** Accurately weighed patches were placed in a desiccators containing anhydrous calcium chloride. After 3 days, the desiccated patch were taken out and subjected to weighing. The formula is:

$$\%\text{moisture loss} = \frac{\text{initial wt - final wt}}{\text{final wt}} * 100$$

- **In Vitro Drug Release Studies:** Franz-diffusion cell was used in our studies for in-vitro drug release. The cell consists of two chambers, the donor and the receptor. The donor compartment is open at the top and is exposed to the atmosphere. The receptor compartment is surround contain a water jacket for maintaining the temperature at 37^0 c ± 2 and is provided with a sampling port. The diffusion medium was pH 7.4 buffer, which was stirrer. The diffusion media was stirred to prevent the formation of concentrated drug solution just beneath the membrane. Sample from the receptor compartment were taken at various intervals of time over a period of 24 hours and the concentration of the drug was determined by UV spectrophotometric at max 244 nm, method using the standard curve. Amount of drug diffused at various time intervals was calculated and plotted against time.

Table 2: In- Vitro Diffusion Study of Ketoconazole [F1-F3]

Time (hr.)	% Drug Release		
	F1	F2	F3
1	9.34	8.7	8.36
2	15.09	15.4	12.3
3	22.89	23.15	21.17
4	29.15	30.22	29.2
5	35.12	36.15	35.89
6	43.22	44.81	42.2
7	50.17	52.17	49.73
8	59.8	60.3	61.27
9	61.50	63.13	62.45
10	67.24	69.95	66.24
11	70.47	72.86	71.37
12	72.67	73.75	75.27
24	81.84	85.33	88.29

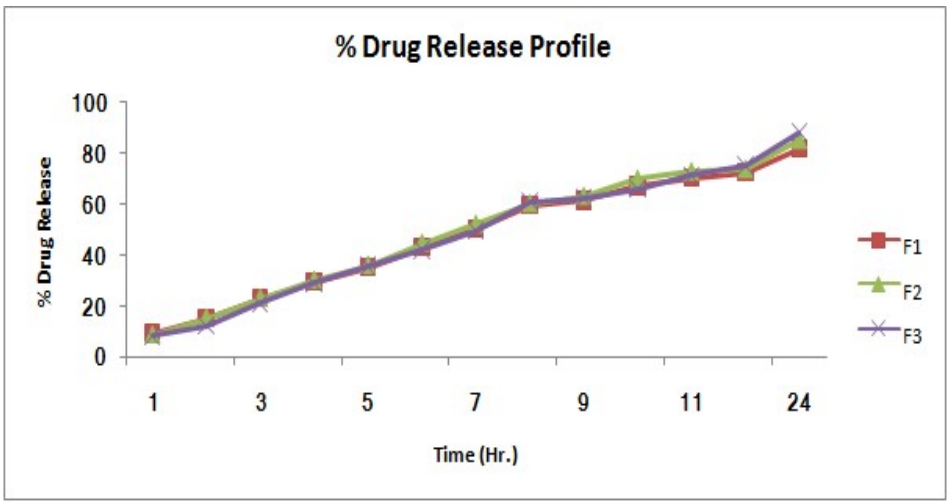

Figure 4: % of Drug Release of F1, F2,F3 Batches.

Table 3: In-Vitro Diffusion Study of Ketoconazole [F4-F6]

Time (hr.)	% Drug Release		
	F4	F5	F6
1	7.4	6.4	9.12
2	18.05	19.1	17.12
3	20.24	22.82	25.36
4	27.2	30.58	32.14
5	35.24	38.57	40.12
6	43.25	46.28	49.8
7	52.55	54.86	55.36
8	57.05	60.5	61.24
9	64.48	66.39	68.65
10	70.18	72.98	75.71
11	77.61	79.87	81.32
12	82.98	84.87	85.22
24	92.17	93.88	94.74

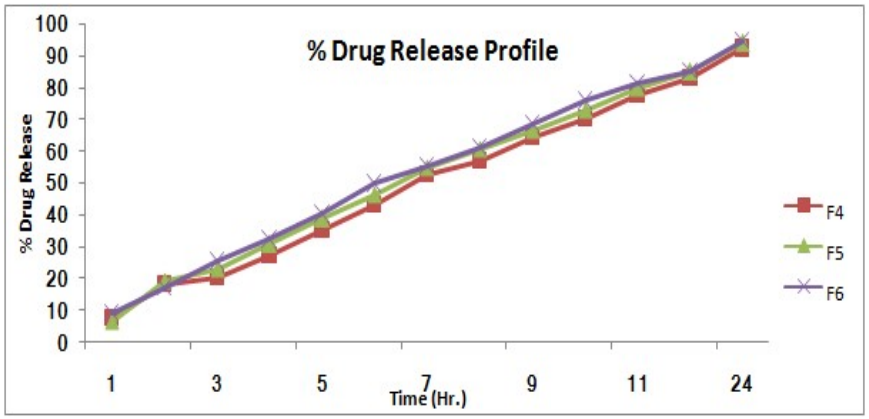

Figure 5: % of Drug Release of F4, F5, F6 Batches.

Table 4: Physico-Chemical Parameters of Prepared Ketoconazole Nail Patches

Patch	Mean Thickness (mm) n=6	Mean Weight(gm) n=6	Mean Folding Endurance	Drug Content (%)
F1	0.039±0.022	0.070±0.033	21±0.71	95.66
F2	0.039±0.020	0.073±0.022	35±0.80	96.09
F3	0.039±0.030	0.072±0.039	34±0.77	95.44
F4	0.039±0.015	0.070±0.028	20±0.76	95.87
F5	0.040±0.010	0.074±0.052	55±1.5	96.94
F6	0.040±0.058	0.075±0.042	62±0.23	97.30

RESULT AND DISCUSSION

Topical drug delivery is especially suitable for onychomycosis and nail psoriasis, which affect 2- 13% and 1 - 3% of the general population, respectively, and make up the bulk of nail disorders. Topical therapy would avoid the adverse events and drug interactions of systemic antifungal agents and the pain of injection when anti psoriatic agents are injected into affected nail folds. However, successful topical therapy is extremely challenging due to the very low permeability of the nail plate. In the present study an attempt has been made to prepare medicated Nail patch using hydrophilic polymers HPMC K 100 & Eudragit. Ketoconazole is the drug of choice for the treatment of onychomycosis due to its efficient anti-

fungal action on causative organisms. Total six medicated Nail patch preparations Ketoconazole of were prepared & evaluated for various parameters i.e., thickness, weight variation, drug content, folding endurance as shown in table-4.

In-Vitro Drug Diffusion Study

Results of in-vitro drug released from different formulations are shown in Table- 2, 3 and graphically shown in Figure 4, 5. The prepared formulations F6 shows better release profile as compare to other preparations i.e., F1, F2, F3 & F4, F5.

CONCLUSIONS

All formulation also showed good physicochemical properties like thickness, weight variation, drug content, folding endurance, moisture content and moisture uptake. The *In-vitro* release data showed that drug release from the patch formulation have been affected by types of polymer and concentration of polymer. Increase the concentration of polymer also increase prolonged drug release. Effect of penetration enhancer i.e., Propylene glycol by checked on in-vitro permeation of drug.

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