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# DEVELOPMENT AND EVALUATION OF KETOCONAZOLE DRUG LOADED TRANSDERMAL PATCHES FOR ANTIFUNGAL ACTION

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## ABSTRACT

Ketoconazole is an antibiotic used to treat certain infections caused by bacteria, such as pneumonia, bronchitis, ear infection, sinusitis, pharyngitis, tonsillitis, and skin fungal infections. In this study, Ketoconazole was used to prepare transdermal patches using various polymers such as Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Glycerine and Dimethyl Sulfoxide with their different concentration. Patches were prepared by the solvent Casting technique. Dimethyl sulphoxide was used to enhance the transdermal permeation of ketoconazole. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance and percentage of moisture content. All prepared formulations indicated good physical stability.

**Keywords: Antifungal Activities, Ketoconazole, Transdermal Patches, Transdermal Film, in-vitro Permeation Study**

## 1. INTRODUCTION:

Skin fungal infections are widely spread all over the world for both sexes including different types related to various pathogens. Tinea is considered one of the most common long-lasting cutaneous fungal infection **[1]**. The primary line of treatment for this type of infection is the topical antifungals while systemic antifungals are suggested in severe or persistent cases **[2]**. Topical antifungal agents are usually favoured over systemic ones due to direct localization of the drug to the infected site, with reduced side effects and enhanced patient compliance **[3]**. Azole antifungals are the most widely used class in treatment of this type of infection. The effective

topical dosage forms including creams, lotions and ointments are applied daily for different time periods. Ketoconazole belonging to azole antifungals is successfully used for the treatment of Tinea fungal infection. It has intermediate molecular weight, good polymers compatibility, low irritation viability and good skin permeability **[4]**. However, the outermost layer of the skin named the stratum corneum acts as the main obstacle for drug penetration. Therefore, studies focus on designing drug delivery systems with improved penetration ability through the stratum corneum to enhance the antifungal efficacy **[3, 5]**.

A transdermal patch is a medicated adhesive patch placed on the skin to deliver a time-released dose of medication through the skin for treating topical or systemic illness. Since early 1990, this dosage form of transdermal therapeutic system has been available in the pharmaceutical market. Such a system offers a variety of significant clinical benefits over others, such as tablet and injection **[6, 7, 8]**. Transdermal drug delivery system (TDDS) can deliver certain medication to systemic circulation in a more convenient and effective way than is possible with conventional dosage form. The potential of skin as a path of drug administration has been amply demonstrated by the acceptability of marketed therapeutic systems **[9]**. Administration of systemic drugs using a transdermal patch represents a non-invasive route, with improved patient compliance. This route of administration prevents passage through the gastrointestinal tract and maintains constant plasma levels for prolonged periods of time **[10]**. Also, for the transdermal route of administration, peak plasma levels of drug are reduced leading to decreased side-effects and it avoids presystemic and systemic first pass metabolism and eliminates the need for intravenous access **[11, 12, 13]**.

Transdermal route is a potential mode of delivery of lipophilic drugs in the systemic circulation **[14]**. It controls of the area of application, amount applied, release kinetics and prolongation of application time **[15]**. Low turnover rate of transdermal products from pharmaceutical research and development departments could be attributed to the disadvantages encountered with this route of administration including the outermost stratum corneum layer of the epidermis as a significant barrier to penetration across the skin, **[16]** skin irritation associated with some drugs, **[17]** limitation of dose that could be incorporated in the patch, lag time for drug absorption and onset of action, and metabolism of some drug in the skin **[18]**.

In this article attempt has been made to fabricate transdermal patches of ketoconazole by using polymer like HPMC

and ethyl cellulose to provide sustained or controlled release of incorporated drug ketoconazole.

## 2. MATERIALS AND METHODS:

**2.1 Materials:** The drug ketoconazole procured from Aarti Drug Limited., Mumbai. The materials used in this study were following: Ketoconazole as drug, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Glycerine and Dimethyl Sulfoxide as plasticizer. Dimethyl sulphoxide was used to enhance the transdermal permeation of Ketoconazole. All other laboratory materials were of analytical grade.

**2.2 Preformulation Study of Ketoconazole:**

**2.2.1 Physical Appearance:** Different organoleptic properties like appearance, colour, odour and taste were determined.

**2.2.2 Determination of Melting Point of Drug:** Melting point of drug sample was performed by using capillary tube method.

**2.2.3 Solubility Studies:** The solubility has been determined after shaking a saturated solution of the drug for 2 hrs at 25° C in water, methanol, ether, acetone, acetonitrile and hexane, respectively.

**2.2.4 Determination of partition co-efficient:** Standard plots of drug were prepared from both the distilled water and octanol. Equal volumes (10ml each) of the two phases were taken in triplicate in conical flask and to each 100mg of weighed amount of drug were added. The flasks were shaken at 32°C for 6h to achieve a complete partitioning at 100 rpm. The two phases were separated by centrifugation at 100rpm for 5min and they were then analyzed for respective drug contents. The partition co-efficient of drug Ko/w was calculated using the following formula.

Ko/w = Concentration in octanol / Concentration in distilled water

**2.2.5 UV Spectroscopy of Drug:**

**i) Determination of λmax Ketoconazole:** The stock solution of ketoconazole was prepared using 100mg in 100 ml of PBS 7.4 in 100 ml of volumetric flask. From this stock solution 1-10 µg/ml concentration range solution were 1µ resulting solution scanned between 225nm on Shimadzu 1700 EUV Spectrophotometer against PBS solution as a blank. The absorption maxima of ketoconazole were found to be 225 nm **[19]**.

**2.2.6 FTIR Spectroscopy:** Fourier transform infrared spectroscopy (FT-IR, Shimadzu, Model-RT-IR-8300) is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm$^2$; the spectra were scanned over the wave number range of 3600 to 400 cm$^{-1}$ at the ambient temperature.

**2.2.27 X-ray Diffraction Technique:** X-ray powder diffraction (XRD) pattern was operated on a Japan RigakuD/Maxr-A X-ray diffractometer equipped with graphite monochromatized high-intensity Cu K radiation (= 1.54178Å). The morphologies of the layers were recorded with a JEM 2100 high resolution transmission electron microscope (HRTEM).

**2.3 Formulation of Transdermal Patches:** In the present study, matrix type transdermal patches of ketoconazole were prepared by moulding techniques. A flat circular glass moulds having diameter 4.5 cm and height of 1 cm with a total surface area of 15.91cm$^2$ was fabricated for this purpose.

**2.3.1 Preparation Of Casting Solutions:** The casting solutions were prepared by dissolving weighed quantities of polymers in a solvent mixture of chloroform and methanol at 1:1 ratio. The drug, plasticizer and permeation enhancers were then added to the various polymer solutions individually and thoroughly mixed to from a homogenous mixture. It was placed aside without any disturbances to allow the entrapped air to bubble out.

**2.3.2 Preparation Of Transdermal Patches:** About 3 ml of casting solutions were pipetted into circular glass moulds especially designed to hold contents, which is casted on mercury surface. The glass moulds containing the casting solutions were allowed for drying at room temperature for 24 hrs and the patches are dried in over at 40-45° for 30 minutes in order to remove the residual solvents. The patches were removed and cut into circular discs with 4.4 cm diameter (15.21cm$^2$ surface area). These patches were wrapped in aluminum foil and stored in dessicator for further studies. The composition of the prepared transdermal patches were given in **Table 1 [20]**.

**Table 1: Compositions of Transdermal Patches**

| Formula code | Drug (mg) | HPMC | EC | Glycerol in % w/w | DMSO in w/w |
|---|---|---|---|---|---|
| KTP1 | 100 | 0.5 | 0.5 | 30 | 20 |
| KTP2 | 100 | 1.0 | 1.0 | 30 | 20 |
| KTP3 | 100 | 1.5 | 1.5 | 30 | 20 |
| KTP4 | 100 | 2.0 | 2.0 | 30 | 20 |
| KTP5 | 100 | 2.5 | 2.5 | 30 | 20 |
| KTP6 | 100 | 0.5 | - | 30 | 20 |
| KTP7 | 100 | 1.0 | - | 30 | 20 |
| KTP8 | 100 | 1.5 | - | 30 | 20 |
| KTP9 | 100 | 2.0 | - | 30 | 20 |
| KTP10 | 100 | 2.5 | - | 30 | 20 |
| KTP11 | 100 | - | 0.5 | 30 | 20 |
| KTP12 | 100 | - | 1.0 | 30 | 20 |
| KTP13 | 100 | - | 1.5 | 30 | 20 |
| KTP14 | 100 | - | 2.0 | 30 | 20 |
| KTP15 | 100 | - | 2.5 | 30 | 20 |

**10% w/w of HPMC: EC, EC= Ethyl cellulose, DMSO= Dimethyl sulphoxide, HPMC= Hydroxy Propyl methyl cellulose**

**2.4 Evaluation Of Transdermal Patches:**

**2.4.1 Physical Appearance:** All the prepared patches were visually inspected for color, clarity, flexibility, and smoothness.

**2.4.2 Film Thickness:** The thickness was measured at six different places using an Electronic Digital Micrometer (AEROSPACE- CHINA) and the mean Value was calculated **[21]**.

**2.4.3 Average Weight and Weight Variation:** As weight variation between the formulated patches can lead to difference in drug content and in-vitro behaviour, a study was carried out by weighing 6 patches in an electronic balance. The average weight of a patch **[22]** and its standard deviation was calculated by using the following formulas.

Average weight of each patches = total weight of 5 patches/5

$$\text{Standard deviation} = \sqrt{\frac{\sum (x-X)^2}{n-1}}$$

**Where x = weight of individual patch, X = average weight, n = number of patches**

**2.4.4 Determination of Tensile Strength:** The instrument, which was designed in our laboratory, was used for the measurement of tensile strength. The strip was clamped at the static end and was attached to the movable rod on a railing with the help of a clip. The weights were gradually added to the pan to increase the pull force till the film was cut. The elongation was determined simultaneously by noting the distance traveled by the pointer, before break of the film, on the graph paper **[23]**. The weight required to break the film was noted as the break force (table 6). The tensile strength was calculated using Allen's formula.

Tensile Strength = Break Force x (1 + ΔL) / a x b L

**2.4.5 Folding Endurance:** Folding endurance of the film is determined by repeatedly folding one film at the same place till it broke , which was considered satisfactory to reveal good films properties. The number of times of films could be folded at the same place without breaking gave the value of the folding endurance. This test was done on randomly selected three films from each formulation.

**2.4.6 Determination Of Percentage Moisture Content:** Moisture content can influence the mechanical strength and drug release behaviour of the transdermal therapeutic systems and therefore, in the present study determination of the moisture of the formulated patch was estimated by keeping the patch under vacuum desiccation until constant weights were obtained **[24]**. The percentage moisture content of the patch was calculated by the following formula.

Percentage moisture content =Initial weight- Final weight / Initial weight

**2.4.7 Determination Of Percentage Moisture Uptake:** The weighed films kept in a desiccator at room temperature for 24hrs was taken out and exposed to 75% relative humidity (a saturated solution of sodium chloride) in a desiccator until a constant weight for the film was calculated as the difference between final and initial weight with respect to initial weight.

Percentage moisture uptake =final weight-initial weight / final weight

**2.4.8 Determination Of Drug Content:** A formulated patch having 15.21 $cm^2$ area was cut into small pieces and transferred into a graduated glass stoppered flask, which contained 100ml of mixture of chloroform and methanol in the ratio of 1:1, maintained at 45-50˚C. It was closed and Shaked vigorously for 24 hours period in a shaker. The solution was filtered and the amount of drug present in the filtrate was determined by using SHIMADZU UV-1700 spectrophotometer. Similarly, blank solution was prepared using a dummy patch. The procedure was carried out in duplicate to determine the drug content **[25]**.

**2.4.9 In-Vitro Drug Release Studies:** In vitro permeation studies were performed by using Franz diffusion cell. It consists of a donor compartment and a receptor compartment. The cellulose membrane was mounted between the donor compartment and receptor compartment of the diffusion cell. The formulated patches were placed over the membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the temperature was maintained at 37±1 °C. The samples were withdrawn at different time intervals and analyzed for drug content **[26]**. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The cumulative percentage release of drug permeated per $cm^2$ of patches were plotted against time.

**2.4.10 Stability Studies:** Scientific data pertaining to the stability of a formulation leads to the prediction of the expected shelf life of the proposed product and when necessary to the reformulation of the dosage form **[27]**. Hence to assess the stability the selected films were kept at room temperature and at 40ºC over a period of 45 days. Patches were evaluated at 15th, 30th, 45th day for their physical appearance.

**3. OBSERVATION:**

**3.1 FTIR Spectra of Drug:** The FTIR spectra of pure drug ketoconazole were showed in **Figure 1** and interpretation of FTIR was showed in **Table 5**.

All characteristics peaks of drug matched with reference spectra of pure ketoconazole.

**3.2 X-Ray Diffraction (XRD):** The XRD spectra of drug was showed in **Figure 2**.

**3.3 Formulation Development:** The photograph of transdermal patches was showed in **Figure 3**. The prepared patches were smooth, translucent and elastic.

**3.4 Physico-Chemical Parameters:** Physiochemical parameter of transdermal patches were mentioned in **Table 5, 6**.

**3.5 In Vitro Drug Release Studies:** In vitro drug release profile were showed in **Figure 4, 5, 6**. All prepared transdermal patches of ketoconazole showed prolonged release of the drug upto 24 hours without reaching plateau.

**3.6 Stability Studies:** The stability study of transdermal patches was showed in **Table 7**.

After a period of 45 days no change was observed in flexibility, transparent, and smoothness of prepared patches. Hence the patches were found to be stable after a period of 45 days.

**Table 2: Physical Properties and Melting Point of Ketoconazole**

| Drug | Parameter | Observation |
|---|---|---|
| Ketoconazole | Colour | White crystalline powder |
| | Odour | Odourless |
| | Taste | Tasteless |
| | Melting point | 149.6 °C |

**Table 3: Solubility of Drug in Different in Different Solvent**

| Drug | Solvent | Solubility |
|---|---|---|
| Ketoconazole | Deionized water | Practically insoluble |
| | dichloromethane | Freely Soluble |
| | Methanol | Soluble |
| | Ethanol | Sparingly Soluble |

**Table 4: Partition Coefficient of Ketoconazole**

| Drug | Solvent | logP |
|---|---|---|
| Ketoconazole | n-Octanol | 4.25 |
| | Distilled water | |

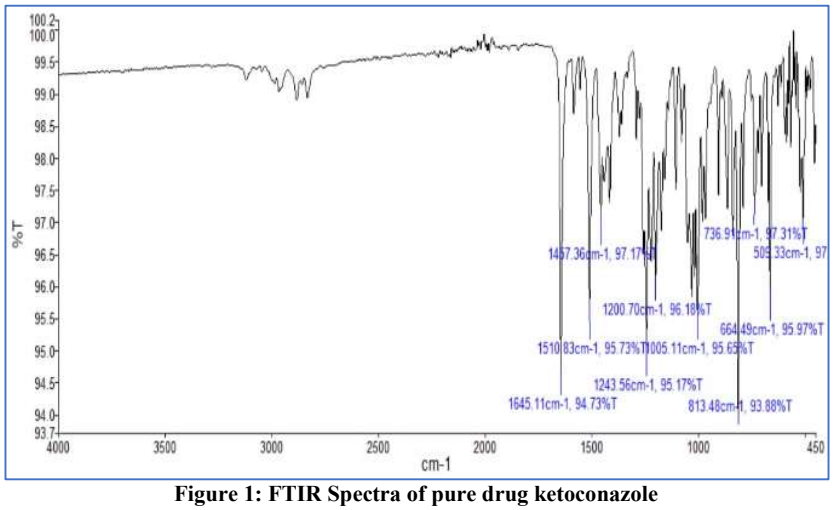


**Figure 1: FTIR Spectra of pure drug ketoconazole**

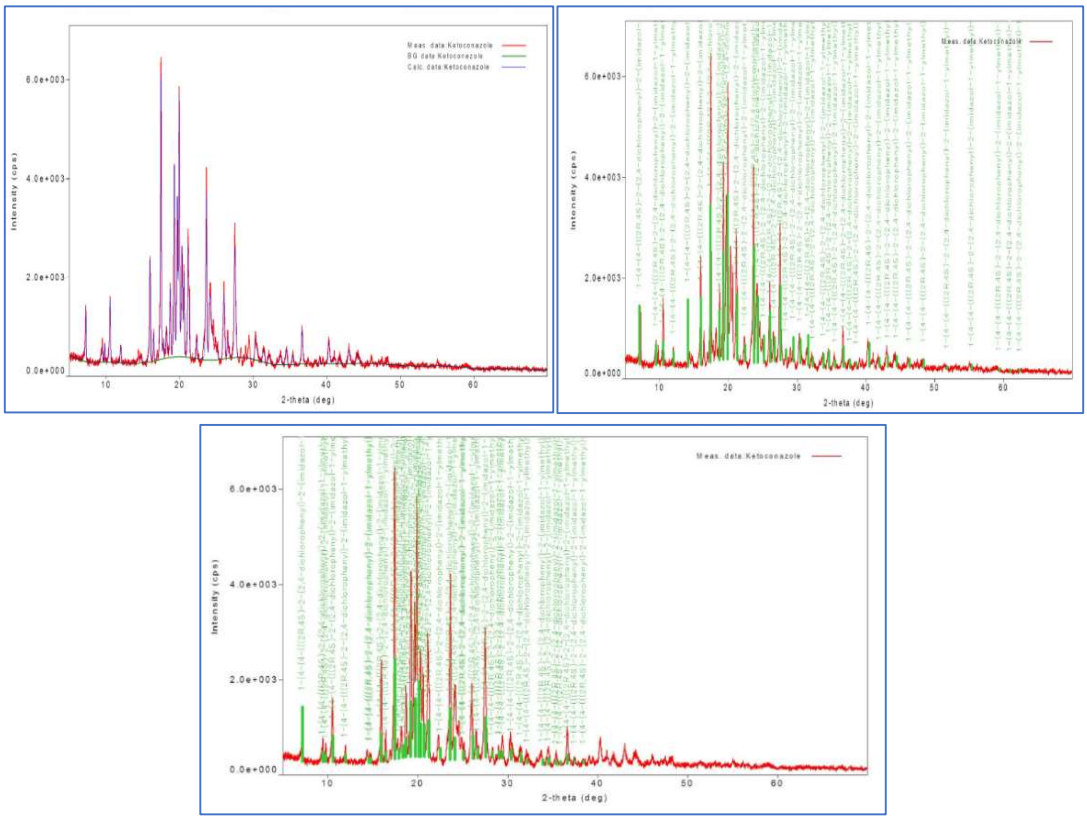


**Figure 2: XRD of Ketoconazole**

**Figure 3: Transdermal Patches of Ketoconazole**

**Table 5: Physical Appearance, Folding insurance and Weight Variation**

| Formula code | Physical Appearance | Folding Insurance | Weight Variation |
|---|---|---|---|
| KTP1 | Transparent, Flexible, Smooth | 4.24±0.12 | 0.332±0.005 |
| KTP2 | Transparent, Flexible, Smooth | 4.28±0.22 | 0.330±0.005 |
| KTP3 | Transparent, Flexible, Smooth | 4.55±0.32 | 0.229±0.006 |
| KTP4 | Transparent, Flexible, Smooth | 4.71±0.50 | 0.331±0.004 |
| KTP5 | Transparent, Flexible, Smooth | 4.65±0.34 | 0.329±0.005 |
| KTP6 | Transparent, Flexible, Smooth | 4.67±0.51 | 0.333±0.004 |
| KTP7 | Transparent, Flexible, Smooth | 4.65±0.52 | 0.327±0.005 |
| KTP8 | Transparent, Flexible, Smooth | 3.99±0.21 | 0.328±0.005 |
| KTP9 | Transparent, Flexible, Smooth | 4.08±0.78 | 0.330±0.004 |
| KTP10 | Transparent, Flexible, Smooth | 4.21±0.12 | 0.331±0.006 |
| KTP11 | Transparent, Flexible, Smooth | 4.78±0.52 | 0.332±0.006 |
| KTP12 | Transparent, Flexible, Smooth | 4.61±0.65 | 0.329±0.005 |
| KTP13 | Transparent, Flexible, Smooth | 4.98±0.52 | 0.328±0.004 |
| KTP14 | Transparent, Flexible, Smooth | 4.53±0.62 | 0.330±0.003 |
| KTP15 | Transparent, Flexible, Smooth | 4.98±0.59 | 0.331±0.004 |

**Table 6: Thickness, Tensile Strength Moisture content, moisture uptake and Drug Content**

| Formula code | Thickness (mm) | Tensile Strength (kg/cm$^2$) | Moisture Content (%) | Moisture Uptake (%) | Drug Content (mg/cm$^2$) |
|---|---|---|---|---|---|
| KTP1 | 0.155±0.022 | 1.756 | 8.76±0.016 | 10.12±0.006 | 0.5634 |
| KTP2 | 0.155±0.021 | 1.746 | 8.45±0.011 | 9.94±0.009 | 0.5643 |
| KTP3 | 0.143±0.026 | 1.746 | 7.99±0.017 | 9.62±0.006 | 0.5621 |
| KTP4 | 0.141±0.019 | 1.747 | 8.01±0.018 | 9.99±0.010 | 0.5628 |
| KTP5 | 0.149±0.024 | 1.748 | 8.45±0.017 | 10.98±0.011 | 0.5629 |
| KTP6 | 0.152±0.024 | 1.739 | 7.23±0.015 | 9.42±0.007 | 0.5623 |
| KTP7 | 0.155±0.023 | 1.775 | 7.85±0.014 | 9.28±0.005 | 0.5645 |
| KTP8 | 0.149±0.019 | 1.756 | 7.45±0.015 | 8.99±0.004 | 0.5631 |
| KTP9 | 0.146±0.018 | 1.734 | 7.89±0.019 | 9.45±0.006 | 0.5599 |
| KTP10 | 0.158±0.019 | 1.723 | 7.87±0.016 | 8.87±0.005 | 0.5601 |
| KTP11 | 0.139±0.019 | 1.715 | 8.14±0.019 | 8.56±0.011 | 0.5621 |
| KTP12 | 0.148±0.021 | 1.709 | 8.23±0.014 | 9.01±0.007 | 0.5642 |
| KTP13 | 0.152±0.016 | 1.699 | 8.24±0.013 | 8.82±0.006 | 0.5639 |
| KTP14 | 0.156±0.0112 | 1.721 | 8.32±0.011 | 9.02±0.008 | 0.5635 |
| KTP15 | 0.159±0.021 | 1.654 | 8.06±0.012 | 9.12±0.005 | 0.5631 |

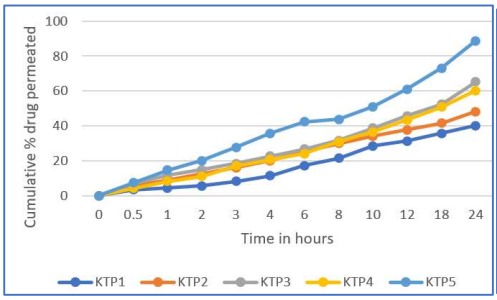


**Figure 4: Cumulative % drug release of formulation KTP1-KTP5**

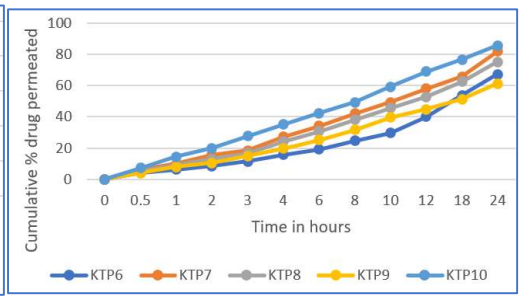


**Figure 5: Cumulative % drug release of formulation KTP6-KTP10**

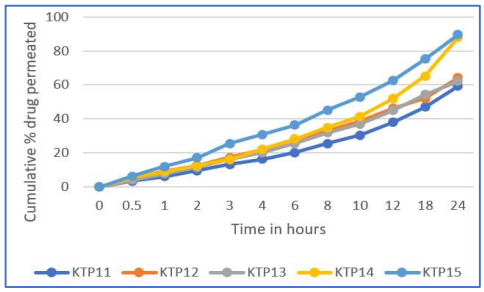


**Figure 6: Cumulative % drug release of formulation KTP11-KTP15**

**Table 7: Stability Study of Transdermal patch**

| Days | Physical Appearance | Weight variation (gm) | Thickness (nm) | Drug content (mg/cm$^2$) | Moisture content (%) | Moisture uptake (%) |
|---|---|---|---|---|---|---|
| 0 | Transparent, Flexible, Smooth | 0.331±0.004 | 0.159±0.021 | 0.5631 | 8.06±0.012 | 9.12±0.005 |
| 15 | No change | 0.330±0.004 | 0.158±0.021 | 0.5630 | 8.04±0.012 | 9.10±0.005 |
| 30 | No change | 0.329±0.004 | 0.158±0.021 | 0.5629 | 8.03±0.012 | 9.08±0.005 |
| 45 | No change | 0.329±0.004 | 0.157±0.021 | 0.5629 | 8.01±0.012 | 9.02±0.005 |

## 4. RESULTS AND DISCUSSION:

**4.1 UV Spectroscopy:** The UV Spectrophotometric method was used to analyze $\lambda_{max}$ Ketoconazole. The absorbance of the drug in phosphate buffered saline pH 7.4 with small amount of methanol was

measured at a wavelength of 225 nm. The lambda max was found in 225 nm.

**4.2 FTIR Spectroscopy:** The IR spectra of pure ketoconazole and polymers were found to be identical. The characteristic IR absorption peaks of 813.48 $cm^{-1}$ C-Cl, 1200 $cm^{-1}$ C-O-C, 1243.56 $cm^{-1}$C=N, 1645 $cm^{-1}$ C=O, 2884-2833 $cm^{-1}$ C-H, 2966 $cm^{-1}$ C-H were present. FTIR spectra of the drug with polymers showed all the ketoconazole characteristics absorption bands suggesting there is no chemical interactions between the drug and polymers used in the formulation. Both the spectra were compared for confirmation of common peaks. Specific peaks of pure ketoconazole loaded patch showed no significant variation in height, intensity and positions of peaks. This confirms that there is no chemical interaction between drug and used polymers as shown in **Figure 1**.

**4.3 XRD Analysis:** XRD analysis revealed that the characteristic intense peaks of pure drug appeared at scattering angles 2 θ of 13.95, 19.99, 22.96, 24.76, 25.4, 27.8, 30.1, 32.5. However, no such intense peaks found at these diffraction angles. The X-ray diffraction patterns of samples are presented in **Figure 2**.

**4.4 Formulation Development:** Transdermal drug delivery system of Ketoconazole was developed using polymers like HPMC, EC, employing glycerine as plasticizer and DMSO as the permeation enhancer. 15 patches of Ketoconazole loaded with different ratios of HPMC, EC were prepared by moulding technique. The prepared patches were evaluated for physico chemical parameters and in vitro drug release behaviour.

**4.5 Evaluation of Patch:** The determination of the average weight of patch, having 14.87 $cm^2$ surface area showed a significant change between the patches prepared with different polymer ratios. The average weight of the patches KTP1- KTP15 were given in the table: 5, 6. Among the 15 patches, KTP1- KTP10 showed a higher average weight compared to other patches and KTP11-KTP-15 showed less weight.

This increase in weight of KTP1- KTP5 patches is due to usage of 10%w/w of polymers whereas in other formulations only 5%w/w polymers were used. There was no significant change in the thickness of the patches (KTP1-KTP15), which was determined by aerospace digital electronic micrometer **(Table 6)**. This indicates that the patches were uniform and reproducible. The results of moisture content **(Table 6)** of the coded transdermal patches (KTP5-KTP10) showed a marked difference in the moisture content. The patches KTP7-KTP15 showed higher moisture content and moisture uptake, which was due to the higher content of hydrophilic polymer, HPMC. The patches KTP1 to KTP5

showed less moisture content and uptake because of the blend of both hydrophobic polymers.

Tensile strength **(Table 5, 6)** is found to be higher for the patches KTP7- KTP15 when compared to other patches and hardness is found to be low for the patches KTP8- KTP15 when compared to other patches. All the patches showed uniform drug content, which was determined using SHIMADZU UV- 1700 spectrophotometer. The folding endurance was found to be 4.24±0.12, 4.21±0.12 and 4.98±0.59 of formulation KTP5, KTP10 and KTP15 respectively. The % moisture content in the patches found from 8.06±0.012- 8.45±0.017. The % moisture uptake in the formulations was in the range of 7.12±0.005 to 10.98±0.011. The thickness in all prepared formulations varied between the range 10.98±0.011 to 0.159±0.021. The tensile strength in all prepared formulations varied between the range 1.699 to 1.775. The Drug Content in all prepared formulations varied between the range 0.5599 to 0.5645.

**4.6 In-vitro drug release study:** The in vitro drug release studies carried out indicate the influence of polymers on the release of drug. The cumulative release of drug (mg/cm$^2$) and cumulative percentage release of KTP1- KTP15 patches over 24 hrs were determined and are summarized in and **Graph 4-6**.

**4.7 Stability Study:** The stability studies indicate there was no change in physicochemical and in vitro drug release studies for KTP10 patches **(Table 7)**.

**5. CONCLUSION:** As far the above results where concerned formulations KTP10 where selected and subjected for stability studies at room temperature and at 40ºC for a period of 45 days. The stability studies results signified that the formulated patches possess adequate shelf life till 45 days. Since the results are encouraging for the formulation KTP10, the proper technique should be applied for commercial and mass production of the same formulation. However long term pharmacokinetic and pharmacodynamic studies should be undertaken to establish the usefulness of these patches.

**6. ACKNOWLEDGEMENT:** Nil

**7. CONFLICT OF INTEREST:** Nil

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