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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF ITRACONAZOLE

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ABSTRACT

Context: To develop low dose maintenance therapy of Itraconazole. **Objetice:** To reduce the risk of potential side effects and to improve the patient compliance. **Results:** Physical appearance of each patch was found to be transparent, uniform and smooth. Thicknesses of all prepared patches were found to be in range of 0.16mm to 0.25mm. Nine formulations (F1- F9) were formulated and evaluated. On the basis of percentage cumulative drug release and folding endurance, F9 formulation was chosen as best formulation. The in vitro drug release profile of optimized formulation was performed in phosphate buffer of PH 7.4. Percent cumulative drug release was found to be 95.42 ± 1.45 at 24 hours. This could be accounted for the slower and control release of drug from transdermal patches.

KEYWORDS: Itraconazole, Transdermal Patch, Thickness, Formulations.

INTRODUCTION

The continuous intravenous (I.V.) infusion has been recognized as a suitable mode of systemic drug delivery that can maintain a constant and sustained drug levels within therapeutic window for long period of time throughout the treatment period. But this mode of drug administration have certain health hazards like accidental needle sticks and needle pain especially for patients requiring multiple administrations on a daily basis, therefore, necessitates of continuous hospitalization during treatment and under medical supervision. It has been realized later that the benefits of I.V. infusion could be closely duplicated without its hassles by using skin as the port of entry of drug. This is known as transdermal administration and the drug therapy systems are known as the transdermal therapeutic

systems or transdermal drug delivery systems or popularly known as transdermal patches.[1]

Transdermal drug delivery systems can deliver medicines via the skin portal to the systemic circulation at a predetermined rate and maintain clinically effective concentrations for prolonged period of time.[2] This route of drug administration represents an attractive alternative to oral delivery of drugs and avoids the hazards and discomfort associated with parenteral therapy. The treatment can also be terminated rapidly by simply removing the patch when need arises.[3]

Nowadays, the transdermal route has become one of the most successful and innovative focus for research in drug delivery with around 40% of the drug candidates being under clinical evaluation related to transdermal or dermal systems.[4] The first transdermal patch of scopolamine was approved in United States in 1979. A decade later, nicotine patches became the first transdermal blockbuster, raising the profile of transdermal delivery in medicine and for the public in general.[5]

MATERIAL AND METHODS

Metrochem API Pvt. Ltd., Hyderabad provided Itraconazole as a gift sample. Nice chemicals provided the Propylene Glycol, Glycerin, Potassium Dihydrogen Phosphate, Chloroform, Aluminium Chloride, Calcium Chloride, Sodium Hydroxide, Hydrochloric Acid. Loba Chemie. Pvt. Ltd. Provided the Hydroxy Propyl Methyl Cellulose and ethyl cellulose.

Preparation of Transdermal Patches

Solvent Evaporation method was used, to prepare the transdermal patches. Itraconazole matrix-type transdermal patches were prepared using ethyl cellulose with HPMC in petri dishes. The Backing membrane was casted by pouring PVA solution in distilled water followed by drying at 60o C for 6 hours in a hot air oven. Polymers were dissolved in chloroform to make a clear solution; glycerin was added as plasticizer and propylene glycol as penetration enhancer. Itraconazole was added and stirred with a mechanical stirrer to get a homogenous dispersion and 2ml of it was cast on prepared PVA backing membrane in each petridish. The rate of evaporation was controlled by inverting a funnel over the petridish and prepared patches were stored in desiccators for further evaluation.

Evaluation of Transdermal Patches of Itraconazole

- **Physical Appearance**: All formulated transdermal patches were visually inspected for colour, clarity, entrapment of any air bubble, flexibility and smoothness.
- **Thickness**: Thickness of each film was measured by using micrometer screw gauge at three different positions of the film and then value was calculated.
- **Surface Analysis by Scanning Electron Microscopy:** The shape and surface characteristics of optimized transdermal patch was analyzed by Field Emission Scanning Electron Microscopy operating at 10 kV. The sample was mounted on an Aluminum stub with adhesive tape and excess samples were removed and coated with gold for 20 seconds. Then the metal stub was placed in E-1010 Ion sputter for 20 minutes under vacuum. After 20 minutes samples were analyzed under Field Emission Scanning Electron Microscope.[6]
- **Weight Uniformity:** Three randomly selected patches were selected and weighed on a digital balance. The average weight with standard deviation was calculated.[7]
- **Percent Elongation:** The percentage elongation was determined by noting the length just before the break point, the percentage elongation was determined from the below mentioned formula given in Eq.1.[8]

Elongation percentage = [(L1−L2)/L2] ×100 (Eq.1)

Where, L1 = Final length of each strip, L2 = Initial length

- **Drug Content Determination:** To determine the drug content of each transdermal patch, weighed portion of Itraconazole patch was cut and dissolve in phosphate buffer pH 7.4 in 100 ml volumetric flask and placed in shaking incubator for 4 h. The solution was filtered through membrane filter (0.45 µm) and 1 ml solution was taken and diluted with phosphate buffer pH 7.4 to 10 ml. The absorbance of solution was measured at 260 nm wavelength by using UV/visible spectrophotometer (Systronics PC Based Double Beam Spectrophotometer 2202). The phosphate buffer 7.4 was used as a blank. The average reading of three patches was taken as the content of drug in one patch.[9]
- **Percent Moisture Absorbed:** To check the physical stability of the patches in high humidity conditions, accurately weighed patches were placed in desiccators containing saturated solution of aluminium chloride (85 ± 5 % RH) for three days. The patches were re-weighed and the percent moisture absorption of each patch was calculated using the formula as given as Eq 2.[10]

Percent Moisture Absorption = Final weight – initial weight × 100 Initial weight (Eq.2)

- **Percent Moisture:** Loss To check the extent of moisture loss from each freshly prepared patch, accurately weighed patches were placed in desiccators containing fused anhydrous Calcium chloride for 72 hrs, the films were reweighed and percent moisture loss was calculated using the formula given in Eq.3.[11]

Percent Moisture Loss = Initial weight – Final weight × 100 Initial weight (Eq.3)

- **Flatness:** Longitudinal strips from the 5 randomly selected transdermal patches were cut out. One from the center and one from the other side of each patch. The length of each strip was measured and the variation in length because of the non-uniformity of flatness was measured. 0 % constriction was considered to be 100 % flatness. Flatness was calculated by measuring constriction of strip using formula given in Eq.4.[12]

Constriction = [(L1−L2)/L2] ×100 (Eq.4)

Where, I1 = Initial length of each strip, I2 = Cutted film length

- **Folding Endurance:** The folding endurance of each patch was expressed as the number of folds (number of times the patch folded at the same place), either to break the preparation or to develop visible cracks. This test was performed to determine the stability of sample to withstand folding and brittleness. Folding endurance of patches were determined by repeatedly folding a small strip of each patch (approximately 2×2 cm) at the same place until it broke. The number of times, patches could be folded at the same place, without breaking gave the value of folding endurance and that was recorded.[13]
- **In Vitro Drug Release:** Study In vitro drug release study was carried out by using Franz diffusion cell. The drug containing film was kept in the donor compartment and was separated from the receptor compartment by egg membrane previously soaked for 24hr in phosphate buffer pH 7.4. The donor and receptor compartments were held together by using a clamp. The receptor compartment with 50ml of phosphate buffer pH 7.4 was maintained at 37±0.50C and stirred with magnetic stirrer. 5ml aliquots were withdrawn at 0, 0.5, 1, 1.5, 2, 2.5,3,6,12, and 24. The samples after filtration were assayed at 260nm spectrophotometrically. Each determination was carried out in triplicate. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the egg membrane was determined as a function of time.
- **Drug Release Kinetics Study:** Drug release is the process by which a drug leaves a drug products and is subjected to absorption, distribution, metabolism and excretion (ADME),

is eventually becoming available for pharmacological action. It is recognized as an important release element in drug development. Under certain conditions, it can be used as a surrogate for the assessment of bioequivalence. The quantitative interpretation of the value obtained in the dissolution assay is facilitated by the usage of generic equation that mathematically translate the dissolution curve in the function of some other parameters related with the pharmaceutical dosage forms. In some cases that equation can be deduced by a theoretical analysis of the process as for example in zero order kinetics.[14]

The method of approach to investigate the Kinetics of release from controlled release.

Statistical method [ANOVA: Two way analysis of variance] and Model dependent method [Zero order, First order, Higuchi, Korsmeyer-Peppas model].

RESULTS AND DISCUSSIONS

- **Physical Appearance:** The prepared transdermal patches were transparent, uniform and smooth. The results of variousbatches are shown in **Table 1.**

Table 1: Physical appearance of Itraconazole loaded transdermal patches.

Formulation code	Physical Appearance
F1	Transparent, uniform and smooth
F2	Transparent, uniform and smooth
F3	Transparent, uniform and smooth
F4	Transparent, uniform and smooth
F5	Transparent, uniform and smooth
F6	Transparent, uniform and smooth
F7	Transparent, uniform and smooth
F8	Transparent, uniform and smooth
F9	**Transparent, uniform and smooth**

- **Thickness:** The thicknesses of all the prepared formulations were in range of 0.16mm to 0.25mm. The results indicated that all the formulations have uniform thickness.

Table 2: Thickness of Itraconazole loaded transdermal patches.

Formulation code	Thickness
F1	0.16 ± 0.01
F2	0.18 ± 0.01
F3	0.25 ± 0.02
F4	0.17 ± 0.04
F5	0.19 ± 0.01

F6	0.23 ± 0.01
F7	0.21 ± 0.03
F8	0.20 ± 0.02
F9	**0.22 ± 0.02**

- **Surface analysis and shape by Field Emission Scanning Electron Microscopy**: Surface morphology of the transdermal patch was examined by FE-SEM as shown in Fig.1. It indicated that the transdermal patch was smooth and contained uniform drug content.

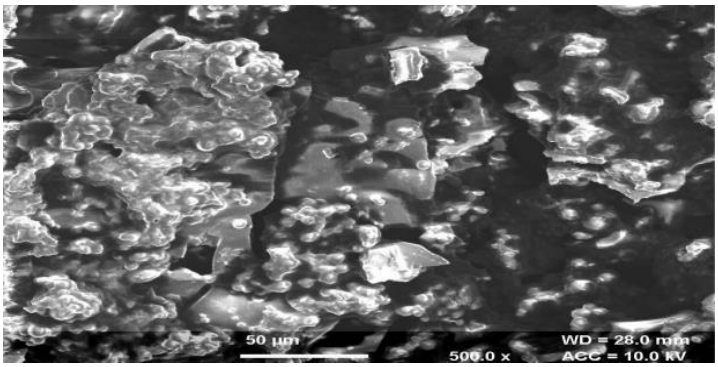

Figure 1: FE-SEM of Itraconazole loaded transdermal patch.

- **Weight Uniformity:** The weights of all the formulations were in the range of 273 ± 2.3mg to 280 ± 1.4mg. The results indicated that the weights of all patches were relatively similar.The results of weight uniformity of nine batches (F1-F9) are summarized in **Table 3.**

Table 3: Weight uniformity of Itraconazole loaded transdermal patches.

Formulation Code	Weight Uniformity(mg)
F1	273 ± 2.3
F2	274 ± 1.4
F3	277 ± 1.2
F4	275 ± 2.1
F5	277 ± 2.5
F6	280 ± 2.11
F7	275 ± 2.4
F8	278 ± 2.5
F9	**280 ± 1.4**

- **Percent Elongation:** The results of % elongation were found to be satisfactory in range of 28.9± 0.015 to 41.2 ± 0.015. The % elongations of nine batches are summarized in **Table 4.**

Table 4: Percent elongation of Itraconazole loaded transdermal patches.

Formulation code	% Elongation
F1	41.2 ± 0.015
F2	38.8 ± 0.014
F3	37.1 ± 0.012
F4	40.2 ± 0.013
F5	39.6 ± 0.017
F6	35.8 ± 0.012
F7	39.2 ± 0.013
F8	28.9 ± 0.015
F9	**30.1 ± 0.015**

- **Drug Content Determination:** The drug content of all formulations was found in range from 91.5 ± 3.62 to 99.5 ± 1.32%. The results indicate good uniformity of drug content in all formulations. Drug content determinationsof nine batches are summarized in **Table 5.**

Table 5: Drug content determination of Itraconazole loaded transdermal patches.

Formulation code	Drug content Determination %
F1	92.2 ± 3.32
F2	93.4± 2.32
F3	98.4± 3.94
F4	96.9± 1.34
F5	94.3± 3.33
F6	97.3± 5.42
F7	92.2 ± 1.32
F8	91.5± 3.62
F9	99.5 ± 1.32

- **Percent Moisture Absorbed:** Percent moisture absorbed of all formulations were found to be in range of 1.45 ± 1.32 to 4.34 ± 2.32.The results indicated that the increase in the concentrations of hydrophilic polymer were directly proportional to the moisture absorbed by the patches. The results of various formulationsare given in **Table 6**.

Table 6: Percent moisture absorbed by Itraconazole loaded transdermal patches.

Formulation code	Percent Moisture Absorbed
F1	4.22 ±0.32
F2	3.94± 0.33
F3	3.81± 0.62
F4	3.72± 0.74
F5	3.51± 0.94
F6	2.97± 0.81

F7	2.7 ± 0.32
F8	2.5± 0.23
F9	**2.4± 0.73**

- **Percent Moisture Lost:** Percent moisture lost of all formulations were found in range of 1.22 ± 1.32 to 4.69 ± 1.33.The results showed good integrity of patches under dry conditions. The results of all formulations aregiven in **Table 7**.

Table 7: Percent moisture lost by Itraconazole loaded transdermal patches.

Formulation code	Percent Moisture Lost
F1	4.11 ±0.51
F2	3.82± 0.23
F3	3.54± 0.85
F4	3.65± 0.24
F5	3.48± 0.94
F6	3.01± 0.24
F7	2.8 ± 0.64
F8	2.7± 0.56
F9	**2.5± 0.71**

- **Flatness:** The results of flatness study showed that none of the formulation had the difference in the strip lengths before and after their cuts, thus indicating 100% flatness. It indicates 0% constriction in the patches and thus they could maintain a smooth surface and lead to better drug permeation. The results of all formulations are shown in **Table 8.**

Table 8: Flatness of Itraconazole loaded transdermal patches.

Formulation code	Flatness %
F1	100%
F2	100%
F3	100%
F4	100%
F5	100%
F6	100%
F7	100%
F8	100%
F9	**100%**

- **Folding Endurance:** The folding endurance was found in range between 180 ± 4 to 220 ± 5, which indicated that the patches would not break and maintain their integrity with general skin folding, when applied. The results of all formulations are shown in **Table 9.**

Table 9: Folding endurance of Itraconazole loaded transdermal patches.

Formulation code	Folding Endurance
F1	180 ± 4
F2	210 ± 5
F3	212 ± 4
F4	190 ± 5
F5	205 ± 5
F6	218 ± 3
F7	195 ± 4
F8	216 ± 4
F9	**220± 5**

- ***In vitro* Drug release Studies:** The results obtained in terms of cumulative drug release after performing *in vitro* dissolutionstudies are tabulated in **Table 10**.

Table 10: *In Vitro* drug release studies of Itraconazole loaded transdermal patches.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	11.1±0.55	12.26±0.68	8.84±0.5	12.96±0.55	13.52±0.95	14.52±0.93	16.73±0.71	12.78±0.80	**11.74±0.83**
1	14.68±0.73	19.80±0.80	16.28±0.51	15.28±0.51	15.28±0.51	13.28±0.51	14.62±1.89	16.15±0.85	**17.54±0.79**
1.5	21.23±0.45	21.50±0.63	23.84±0.42	25.88±0.82	27.88±0.82	28.88±0.82	29.05±0.51	20.32±0.69	**21.55±0.42**
2	30.73±0.42	39.91±0.93	34.52±1.17	36.72±1.15	38.72±1.16	30.72±1.15	31.86±0.68	36.15±0.77	**37.42±0.77**
2.5	31.15±0.67	42.68±0.95	45.72±0.91	44.92±.91	45.92±.61	47.92±.31	49.02±0.72	45.92±0.85	**48.54±0.29**
3	41.97±0.59	59.21±0.79	53.39±0.31	55.59±0.61	56.59±0.72	54.59±0.21	55.76±0.52	54.92±0.71	**53.91±0.53**
6	57.63±0.52	61.95±0.52	69.54±0.98	68.75±0.31	65.75±0.91	65.75±0.45	68.80±0.12	58.75±0.31	**59.72±0.54**
12	72.95±0.51	75.21±0.85	75.37±0.69	77.81±0.60	79.81±0.63	71.81±0.63	73.67±0.65	63.81±0.96	**64.71±0.98**
24	81.71±0.56	83.33±0.91	90.24±1.99	87.24±1.24	91.24±1.54	93.24±1.26	92.42±0.78	92.65±0.89	**95.42±1.45**

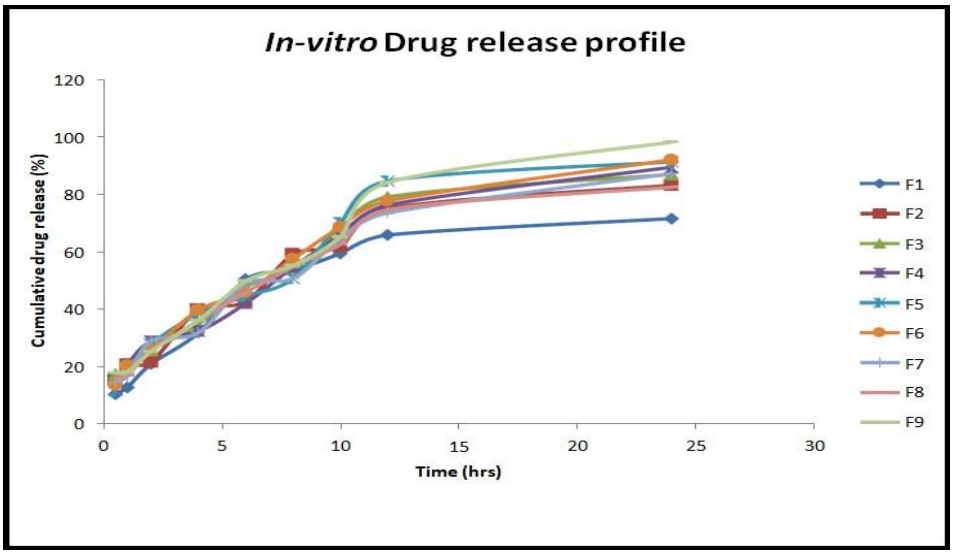

Figure 2: *In vitro* drug release study.

- **Kinetics of drug release:** In order to investigate the release mechanism of present drug delivery system, the data obtained from *in-vitro* release of final optimized batch were

fitted into equations for the zero-order, first-order, Higuchi release model and Korsmeyer-Peppas equation. **Table 11** enlists the values of regression coefficient obtained from various kinetics models.

Table 11: Regression coefficient (R^2) obtained from various kinetics models.

Batch Code	Zero Order Kinetics	Higuchi Kinetics	Korsmeyer-Peppas Kinetics	N	First Order Kinetics
F1	0.834	0.974	0.970	0.610	0.634
F2	0.837	0.968	0.984	0.583	0.710
F3	0.840	0.989	0.953	0.623	0.620
F4	0.859	0.993	0.992	0.562	0.621
F5	0.871	0.978	0.989	0.588	0.671
F6	0.875	0.980	0.989	0.610	0.723
F7	0.863	0.985	0.979	0.567	0.706
F8	0.880	0.990	0.993	0.732	0.693
F9	**0.890**	**0.995**	**0.997**	**0.639**	**0.773**

The interpretation of data was based on the values of the resulting regression coefficients. The *in vitro* drug release showed the regression coefficient values of optimized formulation (F9) for Zero order (R^2= 0.890) shown in **Fig. 3**, Higuchi's model (R^2= 0.995) as shown in **Fig. 4**, Peppas model (R^2= 0.997) and with a value of n = 0.639 as shown in **Fig. 5** and First order (R^2 = 0.773) as shown in **Fig.6**. On the basis of best fit with the highest correlation (R^2) value it is concluded that the optimized formulation of transdermal patch follows the Korsmeyer- Peppas model with release exponent value n = 0.639. The magnitude of the release exponent **n** indicates the release mechanism is Non-fickian diffusion.

Figure 3: Zero plot of the optimized formulation (F9).

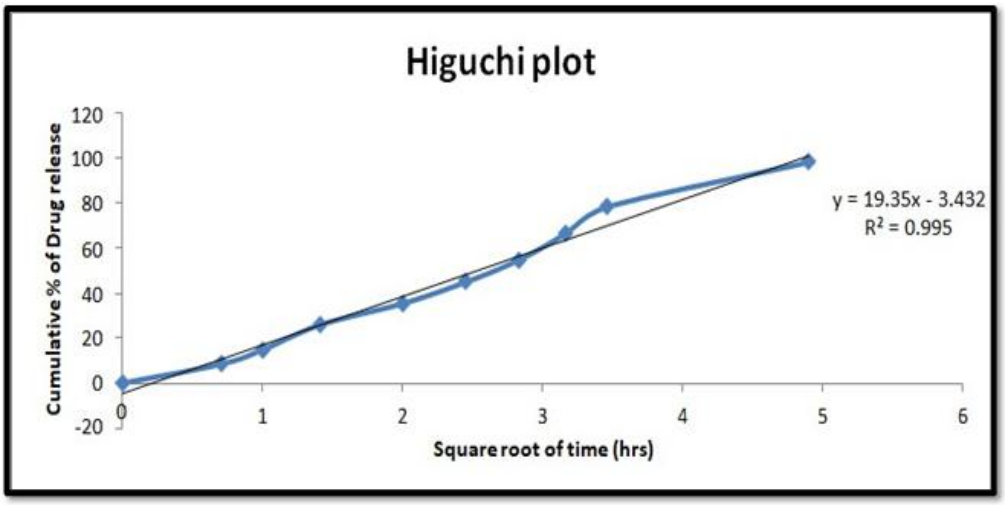

Figure 4: Higuchi plot of the optimized formulation (F9).

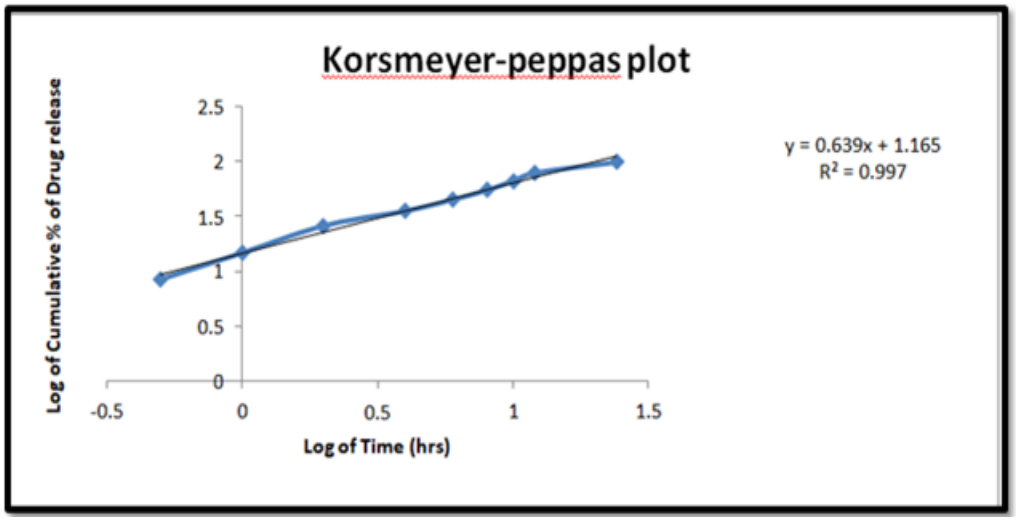

Figure 5: Korsmeyer plot of the optimized formulation (F9).

Figure 6: First order plot of the optimized formulation (F9).

CONCLUSION

From this study, it can be concluded that it is possible to design transdermal patches containing Itraconazole; mainly to be used for various fungal infections. Present study also concluded that as the concentration of hydrophilic polymer and concentration of penetration enhancer increases the cumulative drug release and folding endurance also increases.

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