Development and Characterization of Transdermal Patch of an Antifungal Drug: Itraconzaole

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ABSTRACT

Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal drug delivery systems are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. Transdermal dosage forms, though a costly alternative to conventional formulations, are becoming popular because of their unique advantages. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. Development of controlled release transdermal dosage form is a complex process involving extensive efforts. This review article describes the methods of preparation of different types of transdermal patches, evaluation parameters and some available marketed products. Now a day about 74% of drugs are taken orally and are found not to be as effective as desired either due to bioavailability problems or degradation of drug in acidic pH of stomach. To resolve such problems, transdermal drug delivery system (TDDS) was emerged. Transdermal drug delivery systems are dosage forms involves drug transport to viable epidermal and dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. Transdermal drug delivery systems, also known as ''patches,'' are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. This article provides an overview of TDDS, advantages, limitations, various components of TDDS, methods of preparation, Drug profile, formulation and evaluation of transdermal patch.

Keywords: Itraconazole, Transdermal Patch

INTRODUCTION

Introduction of Transdermal Drug Delivery System
Any drug delivery system aim is to provide a therapeutic amount of drug to the proper site in the body and then maintain desired drug concentration. Drugs are administered by various routes such as oral, parental, nasal, transdermal, rectal, intravaginal, ocular etc. Among all of them, oral route is most common and popular but this route of administration has some drawback like first pass metabolism, drug degradation in gastrointestinal tract due to pH, enzyme etc.[1]

To overcome these drawbacks, a novel drug delivery system (controlled drug delivery system) was developed in which a polymer (natural or synthetic) combined with a drug in such a way that drug is released from the material in a predesigned manner.[1]

The discovery of Transdermal drug delivery system(TDDS) is a breakthrough in the field of controlled drug delivery system. It becomes a great field of interest. TDDS are self-contained, discrete dosage forms which when applied to the intact skin; deliver the drug, through the skin at control rate to the systemic circulation. In 1965 Stoughton first conceived of the percutaneous absorption of drug substances. FDA approved the first Transdermal system Transderm-SCOP in 1979. FDA approved this for the prevention of nausea and vomiting.[1]

In TDDS, the drug is mainly delivered through the skin with the aid of transdermal patch which is a medicament adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and to the blood stream. Now a day TDD is a well-accepted means of delivering many drugs to the systemic circulation in order to achieve a desired pharmacological outcome.[1]

The success of this approach is evidenced by the fact that there are currently more than 35 TDD products approved in the USA for the treatment of conditions including hypertension, angina, female menopause, severe pain states, nicotine dependence, male hypogonadism, local pain control and more recently, contraception and urinary incontinence.[1]

Advantages of TDDS[2]
→ Transdermal medication delivers a steady infusion of a drug over an extended period of time.
→ Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.
→ They are non-invasive, avoiding the inconvenience of Parenteral therapy.
→ The drug input can be terminated at any point of time by removing transdermal patch.
→ The simplified medication regimen leads to improved patient compliance and reduced inter &intra – patient variability.
→ Self-administration is possible with these systems.
→ They can be used for drugs with narrow therapeutic window.
→ Longer duration of action resulting in a reduction in dosing frequency.
→ Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

Disadvantages of TDDS[2]
→ The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10mg/day, the transdermal delivery will be very difficult.
→ Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
→ Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
→ Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
→ The barrier function of the skin changes from one site to another on the same person, from person to person and with age.
→ Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level.
→ The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.
→ The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

Limitations of TDDS[3]
→ The drug moiety must possess some physicochemical properties for penetration through skin and if dose of drug is large i.e., more than 10-25mg/day transdermal delivery is very difficult, daily dose of drug preferred less than 5mg/day.
→ Local irritation at the site of administration such as itching, erythema and local edema may be caused by drug or the excipients used in the formulations.
→ Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
→ Some patients develop contact dermatitis at the site of application due to system components.
→ The barrier function of the skin changes from one site to another, from person to person and with age.
→ Poor skin permeability limits the number of drugs that can be delivered in this manner.
→ A high drug level cannot achieve by this system.
→ Transdermal drug delivery is unable to deliver ionic drugs.
→ Transdermal drug delivery system is restricted to potent drug.
→ It cannot deliver drugs in a pulsatile fashion.
→ Tolerance inducing drugs or those (e.g., hormones) requiring chrono pharmacological management is not suitable candidates.

→   Required significant lag time.

Ideal molecular properties for transdermal drug delivery[4]
- →   An adequate solubility in lipid and water is necessary for better penetration of drug (1mg/ml).
- →   Optimum partition coefficient is required for good therapeutic action.
- →   Low melting point of drug is desired (<200°C).
- →   The pH of the saturated solution should be in between 5 to 9.

Skin As Site for Transdermal Drug Administration[4]

The skin of an average adult body covers a surface area of approximately two square meters and receives about one-third of the blood circulating through the body. The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers: the epidermis, the dermis, and the hypodermis (Fig 1.1).

Microscopically, the epidermis is further divided into five anatomical layers with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment. An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts on each square centimeter of skin area. These skin appendages, however, actually occupy, grossly, only 0.1% of the total human skin surface.

Even though the foreign agents, especially the water-soluble ones, may be able to penetrate into the skin via these skin appendages at a rate which is faster than through the intact area of the stratum corneum, this trans-appendage trans-appendage route of percutaneous absorption has, at steady state, a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecules can thus, be considered as a process of passive diffusion through the intact stratum corneum in the inter follicular region.
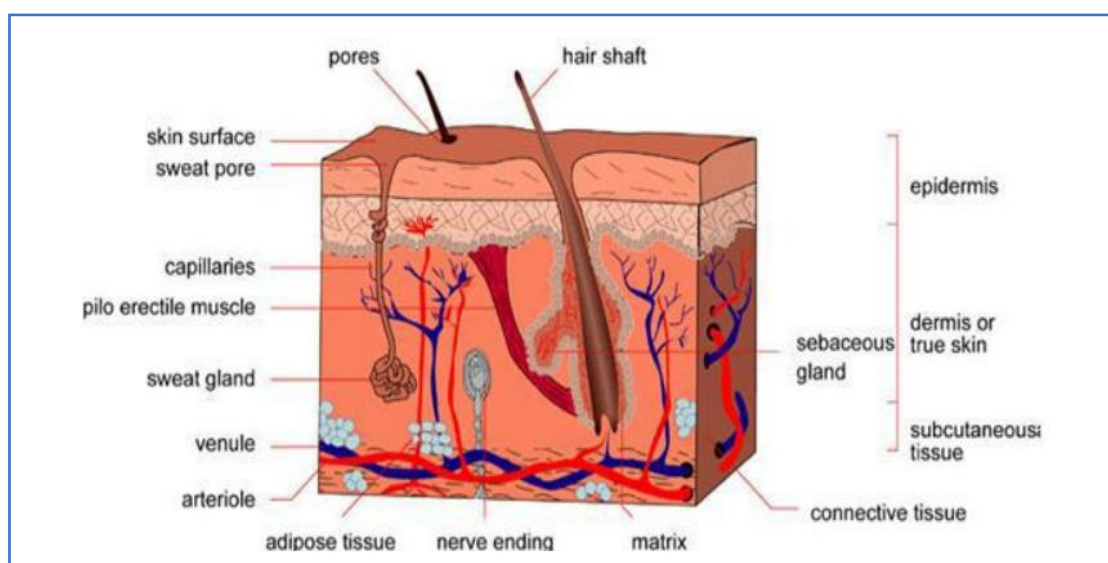

Figure 0.1 Cross section of skin

Basic Component of Transdermal Patch[5]
The component of TDDS Include;
1. Polymer matrix or matrices
2. The drug
3. Permeation enhancers
4. Other excipients
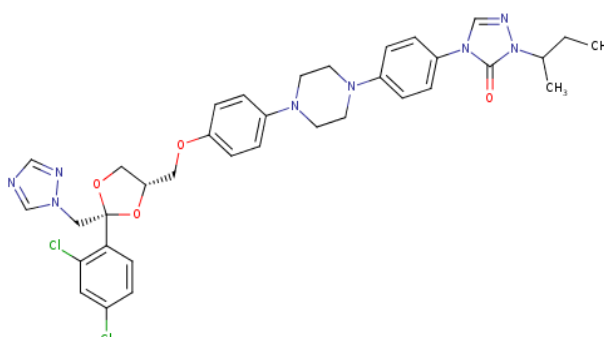
Evaluation of Transdermal Patch[5]
- o   Appearance
- o   Weight Variation
- o   Thickness
- o   Folding Endurance
- o   Tensile strength
- o   % Elongation
- o   Flatness test

- o Surface pH
- o Drug Content
- o Dissolution study
- o Permeability study
- o Skin irritation study
- o Stability studies

INTRODUCTION OF DRUG

- **Itraconazole:** [6-10]

<p align="center">Table 0.1Drug Information</p>

General Properties:	
Name	Itraconazole
Appearance	White
Structure	
Category	Anti-Fungal
Molecular Weight	705.64 g/mol
Chemical Formula	$C_{35}H_{38}Cl_2N_8O_4$
IUPAC Name	1-(butan-2-yl)-4-{4-[4-(4-{[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy} phenyl) piperazin-1-yl] phenyl}-4,5-dihydro-1H-1,2,4-triazol-5-one
Solubility	Its aqueous solubility across the physiological pH range is ~0.04 mg/ml.
Water Solubility	0.00964mg/ml
Log P	5.66
pKa	3.70
Melting point (°C)	166°C
Identification	FTIR, UV
BCS Class	II
Hygroscopic	Non-Hygroscopic
Dose	100/200 mg twice daily

PharmacokineticProperties:	
Absorption	The absolute oral bioavailability of itraconazole is 55%, and is maximal when taken with a full meal.
Bioavailability	55 %
Protein binding	99.8 %
Metabolism	Hepatic
Half life	21 hours
Excretion	Renal
Pharmacological Properties:	
Indication	For the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients: pulmonary and extrapulmonary blastomycosis, histoplasmosis, aspergillosis, and onychomycosis.
Mechanism of action	Itraconazole interacts with 14-α demethylase, a cytochrome P-450 enzyme necessary to convert lanosterol to ergosterol. As ergosterol is an essential component of the fungal cell membrane, inhibition of its synthesis results in increased cellular permeability causing leakage of cellular contents. Itraconazole may also inhibit endogenous respiration, interact with membrane phospholipids, inhibit the transformation of yeasts to mycelial forms, inhibit purine uptake, and impair triglyceride and/or phospholipid biosynthesis.

MATERIALS AND EQUIPMENTS
LIST OF MATERIALS

Table 0.1List of materials

Sr. No.	Material	Role	Sources of Material
1.	Itraconazole	API	Torrent Research Centre, Ahmedabad
2.	Eudragit S100 HPMC E50	Polymers	Balaji Chemicals, Ahmedabad.
3.	PEG400	Plasticizer	Balaji Chemicals, Ahmedabad.
4.	Glycerin	Permeability Enhancer	Balaji Chemicals, Ahmedabad.
5.	Acetone	Solvent	Molychem, Ahmedabad.

LIST OF EQUIPMENT'S

Table0.2 List of Equipment's

Sr. No.	Equipment's	Manufacturers
1.	Digital weighing balance	REPTECH weighing balance ltd.,Ahmadabad
2.	Franz Diffusion Cell	Durasil, Durga Scientific pvt, ltd. Vadodara, Gujarat, India.
3.	U.V. Visible spectrophotometer	Shimadzu-1601, Kyoto, Japan.
4.	FTIR	FTIR8400S, Shimadzu, Kyoto, Japan.
5.	Magnetic stirrer	Megha Enterprise, India.
6.	pH Meter	ELICO, India.

EXPERIMENTAL WORK

PREFORMULATION STUDY
Identification of Drug
Physical appearance, color and nature of drug were evaluated.

Melting Point
Melting point of the drug was determined by capillary method and the temperature at which the drug melts was note down.

Solubility
Solubility study carry out by saturation solubility method in which saturated solution of drug was prepared and transferred in a glass vial. Drug was dissolve in 10 mL of the solvent up to saturation. The solution was sonicating for 15 minutes, than filtered and diluted if required. The amount of the drug dissolved was measure by using UV spectrophotometer. The results of solubility study were recorded.

Compatibility study by FTIR
The FTIR studies were perform by the pressed pellet technique using a KBrpress. The drug powder sample was mix with dried KBr crystals and themixture was press to form pellets using KBr press. The prepared pellet wasplace in the sample holder and kept in the instrument to record the IR peaks. The same method is followed for final formulation.

PREPARATION OF STANDARD CALIBRATION CURVE
Determination of λ_{max} of Itraconazole
Accurately weighed 10mg Itraconazole was transfer to 100 ml volumetric flask and dissolved in 10 ml phosphate buffer 7.4. The volume made up to the mark with phosphate buffer 7.4 to prepare a stock solution of 100 µg/ml. The stock solution was dilute with phosphate buffer 7.4 and was scan for UV spectrum by using Shimadzu UV/Visible double beam spectrophotometer.

Preparation of Calibration curve of Itraconazole
From standard stock solution of 100 µg/ml, Different aliquots of 5,10,15,20 and 25 ml were taken into different volumetric flasks and volume was made up to 100 ml with phosphate buffer pH 7.4 so as to get drug concentrations of 5, 10, 15, 20 and 25 µg/ml respectively. The absorbance of final drug solutions was estimated at λ_{max}.

DOSE CALCULATION
Diameter of the Petri dish = 9.0 cm
Radius = Diameter /2 = 9.0/2 = 4.5 cm.
Area of Petri dish = πr^2 = 3.14 X 4.5 X 4.5 = 63.58 cm^2
Dose is 2.5 mg and film dimension are 2 cm X 2 cm = 4 cm^2
4 cm^2 contain = 100 mg of Itraconazole
Therefore, 63.58 cm^2 contain (?) = 1589.5mg ~ 1590 mg Itraconazole.

FORMULATION OF TRANSDERMAL PATCH OF ITRACONAZOLE
In the present study, matrix type transdermal patches of Itraconazole were prepared by solvent casting techniques. Circular, glass Petri dish having surface area of 63.5 cm^2 were fabricated for casting the patches.
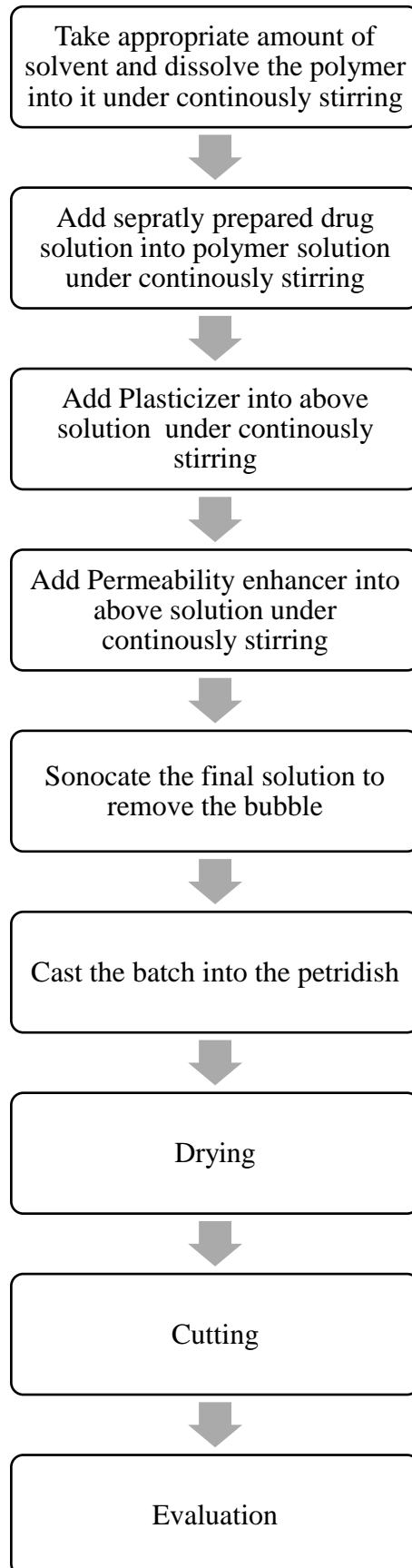
Selection of ingredients
From the literature review and based on the characteristics of Eudragit S 100, it was selected as parentpolymer. The further need was to select polymerwhich can retard the drug release for or near to 8 hrs. Along with Eudragit S100, HPMC E50 LV was selected as release controlling polymer for matrix type Patch. Further, PEG 400 was selected as plasticizer. Glycerin was selected as permeability enhancer.

Table 3.1 Formulation table

Ingredient/ patch (mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14
Itraconazole	100	100	100	100	100	100	100	**100**	100	100	100	100	100	100
HPMC E50	100	200	300	-	-	-	100	**150**	200	175	200	200	150	300
Eudragit S100	-	-	-	100	200	300	200	**150**	100	175	150	200	250	100
PEG 400 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	**0.5**	0.5	0.5	0.5	0.5	0.5	0.5
Glycerin (ml)	1	1	1	1	1	1	1	**1**	1	1	1	1	1	1

Acetone (ml)	-	-	-	10	10	10	10	**10**	10	10	10	10	10	10
Water (ml)	10	10	10	10	10	10	10	**10**	10	10	10	10	10	10

Manufacturing Process Flow chart

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┌─────────────────────────────────┐
│ Take appropriate amount of       │
│ solvent and dissolve the polymer │
│ into it under continously stirring│
└─────────────────────────────────┘
              ↓
┌─────────────────────────────────┐
│ Add sepratly prepared drug       │
│ solution into polymer solution   │
│ under continously stirring       │
└─────────────────────────────────┘
              ↓
┌─────────────────────────────────┐
│ Add Plasticizer into above       │
│ solution under continously       │
│ stirring                         │
└─────────────────────────────────┘
              ↓
┌─────────────────────────────────┐
│ Add Permeability enhancer into   │
│ above solution under             │
│ continously stirring             │
└─────────────────────────────────┘
              ↓
┌─────────────────────────────────┐
│ Sonocate the final solution to   │
│ remove the bubble                │
└─────────────────────────────────┘
              ↓
┌─────────────────────────────────┐
│ Cast the batch into the petridish│
└─────────────────────────────────┘
              ↓
┌─────────────────────────────────┐
│ Drying                           │
└─────────────────────────────────┘
              ↓
┌─────────────────────────────────┐
│ Cutting                          │
└─────────────────────────────────┘
              ↓
┌─────────────────────────────────┐
│ Evaluation                       │
└─────────────────────────────────┘
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EVALUATION OF TRANSDERMAL PATCH OF ITRACONAZOLE

Appearance

Check the visual appearance of the prepared Transdermal patches and record the same.

Thickness

The thickness of the prepared patches was measured using digital Vernier caliper with a least count of 0.01 mm at different spots of the patch. The thickness was measured at three different spots of the patches and average was taken and SD was calculated.

Weight Variation

Four-centimeter square of the patch was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

Folding Endurance

Folding endurance was determined by repeated folding of the patch at the same place till the strip breaks. The number of times the patch is folded without breaking was computed as the folding endurance value.

Surface pH

The surface pH of prepared transdermal patch was determined using pH meter. Patch was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the patch. The procedure was performed in triplicate and average with standard deviation was reported.

Drug Content

Drug content test of the patch was carried out by dissolving the 4 cm^2 patch in 100 ml of pH 7.4 phosphate buffer. The prepared solution was filtered and then measured spectro photo metrically at λ_{max} of 262 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

Percentage Elongation

The percentage elongation was determined by noting the length just before the break point and calculating the same by using below mentioned equation;

Percentage Elongation = (L1-L2/L1) x 100

Where, L1 is the final length of each patch and L2 is the initial length of each patch

***In Vitro* Diffusion Study**

In Vitro Drug Diffusion studies was carried out using the 20 ml Franz diffusion cell. The synthetic membrane was used as a skin. The membrane was stabilized before mounting to remove the soluble components. The membrane was mounted between the donor and receptor compartments. The receptor compartment was filled with 20 ml of isotonic phosphate buffer of pH 7.4 which was maintained at $37\pm 0.2^{o}C$ and hydrodynamics were maintained using magnetic stirrer. One patch of dimension 2 cm $\times$ 2 cm was previously moistened with a few drops of pH 7.4 phosphate buffer and placed in donor compartment. 1 ml samples from receptor compartment were withdrawn at suitable time interval of 1, 2, 3, 4, 6 and 8 hours which was then replaced with 1 ml of pH 7.4 phosphate buffer. The percentage of drug permeated was determined by measuring the absorbance in UVVisible spectrophotometer at λ_{max} of 262 nm.

Stability study

Stability study was carried out at $40^{0}C/75\%$ RH condition for 1 month. Each piece of the patch from the optimized formulation was packed in butter paper followed by aluminum foil. After 1 month, the patches were evaluated for the physical appearance, drug content and diffusion study.

RESULTS & DISCUSSION

PREFORMULATION STUDY

The results of Preformulation study were recorded as below;

- **Appearance of Drug:** White to slightly yellow powder
- **Color of Drug:** White to slightly yellow
- **Physical state:** Crystalline
- **Melting point:** 166 °C
- **Solubility:** Slightly soluble in alcohol, Soluble in acetone and 7.4 phosphate buffer

Obtained results of solubility suggested that Itraconazole freely soluble in distilled water and in phosphate buffer pH 7.4. However, transdermal matrix patch applies on the skin, therefore to evaluate permeation of drug through skin pH, phosphate buffer pH 7.4 was select as a diffusion medium for further study.

Fourier Transform Infra-Red Spectroscopic Studies (FTIR)
FTIR study was performing for the identification of the drug and excipients and to study drug - excipients and excipients - excipients compatibility. FTIR spectra of pure drug and final optimized batch showed in below figure 6.1 and 6.2 respectively. Characteristics peaks obtained for the pure drug correlated well with that of the formulation peaks. This indicated that the drug was compatible with the formulation component
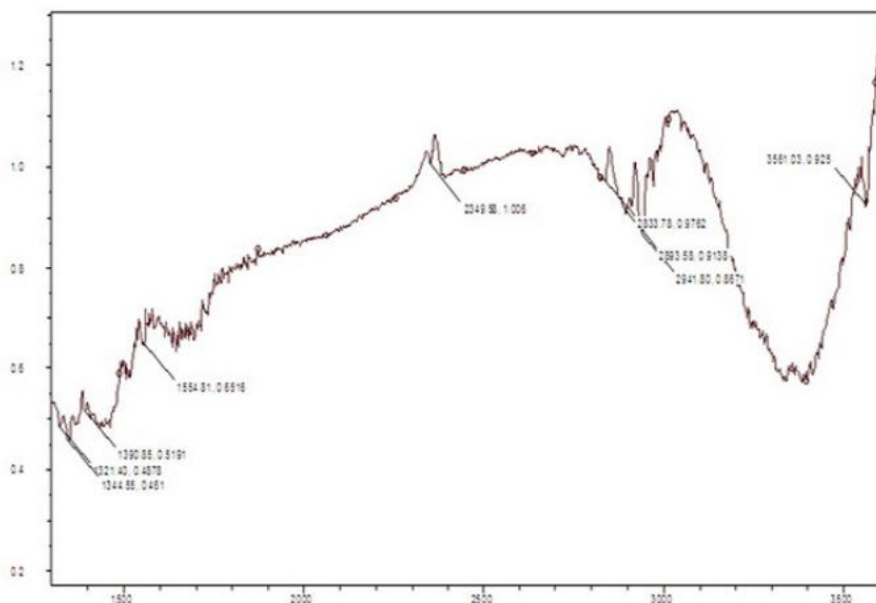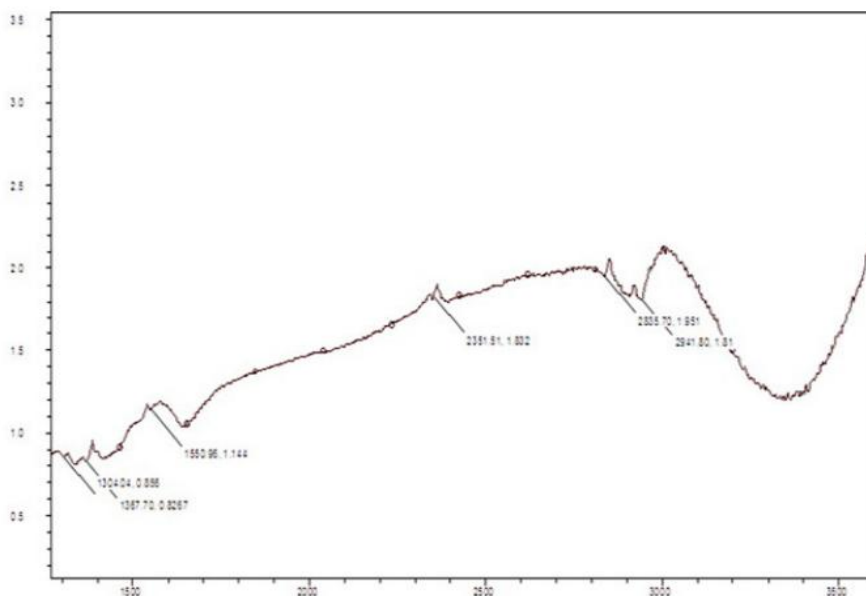

Figure 0.1 FTIR Spectrum of Itraconazole

Figure 0.2 FTIR Spectrum of Final formulation

CALIBRATION CURVE

Itraconazole 20 µg/ml solution was scanned between 400.00 nm - 200.00 nm in UV spectrophotometer by using 7.4 phosphate buffer as blank. The λ_{max} of the drug in 7.4 phosphate buffer was found 262 nm. The same wavelength was selected for further analysis.

Table 0.1 Calibration curve of Itraconazole in 7.4 phosphate buffer

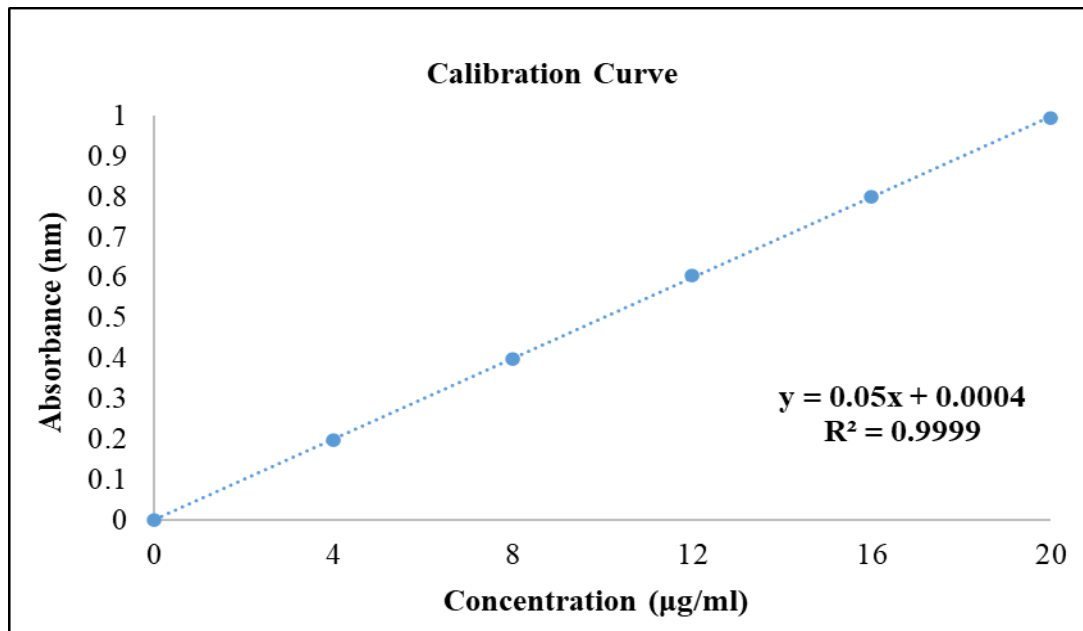| Concentration (µg/ml)	Average Absorbance (nm) ± SD
0	0
4	0.198
8	0.400
12	0.605
16	0.801
20	0.996

Figure 0.3Calibration curve of Itraconazole in 7.4 phosphate buffer

EVALUATION OF ITRACONAZOLE TRANSDERMAL PATCHES

Formulation and development of Itraconazole transdermal patches has been initiated to achieve the targeted objectives. The development batches were taken using HPMC E50 and Eudragit S100 as matrix forming polymers. The evaluation parameters were checked and recorded as below;

Table 0.2Evaluation of Itraconazole Transdermal Patches

Batch	Surface	Transparency	Stickiness
A1			
A2	Smooth	Transparent	Non-Sticky
A3			
A4			

A5			
A6			
A7			
A8			
A9	Rough		
A10			
A11			
A12			
A13			
A14			

Based on the appearance results, it was observed that the all batches were found non-sticky in nature. The patches were transparent and smooth in surface. It was concluded that the all excipients were found in solubilize form and no any undissolved particles are present in the preparation.

Table 0.3 Evaluation of Itraconazole Transdermal Patches

Batch	Weight variation (mg)± SD	Thickness (mm) ± SD	Surface pH± SD
A1	102 ± 3.9	0.21 ± 0.05	7.1 ± 0.2
A2	201 ± 4.1	0.25 ± 0.03	6.9 ± 0.4
A3	299 ± 4.5	0.31 ± 0.04	7.0 ± 0.3
A4	101 ± 2.6	0.22 ± 0.09	7.2 ± 0.4
A5	204 ± 4.8	0.24 ± 0.02	7.1 ± 0.2
A6	301 ± 3.9	0.30 ± 0.03	7.0 ± 0.2
A7	105 ± 3.1	0.21 ± 0.06	6.9 ± 0.3
A8	202 ± 3.6	0.26 ± 0.04	6.9 ± 0.2
A9	300 ± 3.2	0.32 ± 0.02	6.8 ± 0.4
A10	348 ± 2.6	0.34 ± 0.04	6.9 ± 0.1

A11	356 ± 1.9	0.35 ± 0.03	6.8 ± 0.3
A12	405 ± 1.4	0.37 ± 0.02	7.0 ± 0.2
A13	411 ± 3.9	0.37 ± 0.04	6.9 ± 0.1
A14	409 ± 2.8	0.39 ± 0.01	7.1 ± 0.2

Based on the above weight variation, thickness and surface pH results, it was observed that the all A1-A14 batches were found satisfactory in terms of weight variation test.

The weight variation was found well within acceptable range. The thickness of patches was found uniform in nature and the variation is found satisfactory.

Further, the surface pH of the patches was found between 6.8 to 7.1 and it is acceptable.

Table 0.4Evaluation of Itraconazole Transdermal Patches

Batch	Drug Content (%)± SD	Folding Endurance ± SD	% Elongation
A1	98.9 ± 3.1	59 ± 10	2.6 ± 1.1
A2	99.1 ± 2.5	72 ± 12	3.9 ± 1.4
A3	99.4 ± 3.6	91 ± 14	4.1 ± 1.3
A4	98.5 ± 3.3	102 ± 15	5.6 ± 2.4
A5	98.2 ± 3.9	114 ± 12	6.8 ± 3.2
A6	99.5 ± 1.8	130 ± 16	7.2 ± 2.2
A7	98.9 ± 1.3	149 ± 18	10.3 ± 3.3
A8	99.2 ± 3.1	169 ± 14	12.5 ± 3.9
A9	99.7 ± 3.8	190 ± 13	14.8 ± 4.4
A10	97.8 ± 2.9	201 ± 11	15.2 ± 1.9
A11	99.2 ± 2.4	220 ± 10	14.7 ± 2.3
A12	99.8 ± 2.6	296 ± 16	17.9 ± 2.5
A13	98.2 ± 1.9	301 ± 14	18.1 ± 2.1
A14	97.6 ± 1.4	325 ± 19	19.3 ± 1.9

Based on the above results of drug content, folding endurance and % elongation, it was observed that all A1-A14 batches were well within acceptable range of drug content. The % elongation of all batches was recorded in the above table. Based on % elongation results, it was noted that theelasticity of the film was increased with the increase in amount of polymer. Folding endurance of the A1 to A14 batches were found satisfactory. Higher the amount of polymer gives the higher value of folding endurance. Polymers in combination gives high folding endurance as compared to single polymer. However, the Eudragit S 100 gives more folding endurance as compared to HPMC polymer.

Drug release study of all 14 batches was performed to identify the good polymer and plasticizer combination. Initially the trial batches were taken with a single polymer like HPMC and Eudragit S100. The drug release was not achieved as per the target drug release profile for 8 hours. Hence the combination of these two polymers is taken and found better results than the single polymers.

Among all batches, A8 batch which contains HPMC and Eudragit S100 as matrix polymers and PEG 400 as plasticizer gives more than 90% drug release within 8 hours. Further, increase in amount of polymer retard the drug release. As shown in batch A10 to A14 higher amount of polymer not release drug within 8 hours. Hence the desired drug release was expected from HPMC and Eudragit S100 polymers combination. The results were recorded in below table and the comparison also showed in below figure.

Table 0.5 Evaluation of Drug release profile Itraconazole Transdermal Patches

| Time (Hrs.)	1	2	3	4	5	6	7	8
A1	35.9	59.5	76.9	89.5	98.2	99.8	99.9	99.9
A2	32.5	56.7	71.8	84.3	92.8	97.9	98.2	99.7
A3	28.5	52.3	67.2	81.0	89.3	94.2	97.4	98.9
A4	30.2	56.7	69.7	78.3	87.5	92.4	99.7	99.9
A5	26.7	50.9	62.9	73.5	81.6	89.3	98.9	99.7
A6	22.8	47.3	59.2	70.6	76.5	86.7	99.2	99.6
A7	18.9	42.1	54.6	65.9	71.2	80.3	93.4	98.5
A8	21.6	45.9	58.6	68.2	73.3	85.6	92.5	99.7
A9	26.5	48.3	61.3	71.3	77.8	89.3	98.2	98.8
A10	20.9	45.2	54.3	66.1	71.5	80.9	88.3	94.6
A11	18.2	41.3	50.3	61.2	67.5	76.2	82.1	89.9
A12	15.3	35.2	47.2	56.9	64.2	72.3	81.5	88.1
A13	14.1	31.2	44.3	52.3	61.9	70.3	78.9	85.4
A14	11.2	27.3	41.1	49.8	59.1	68.9	75.6	82.6
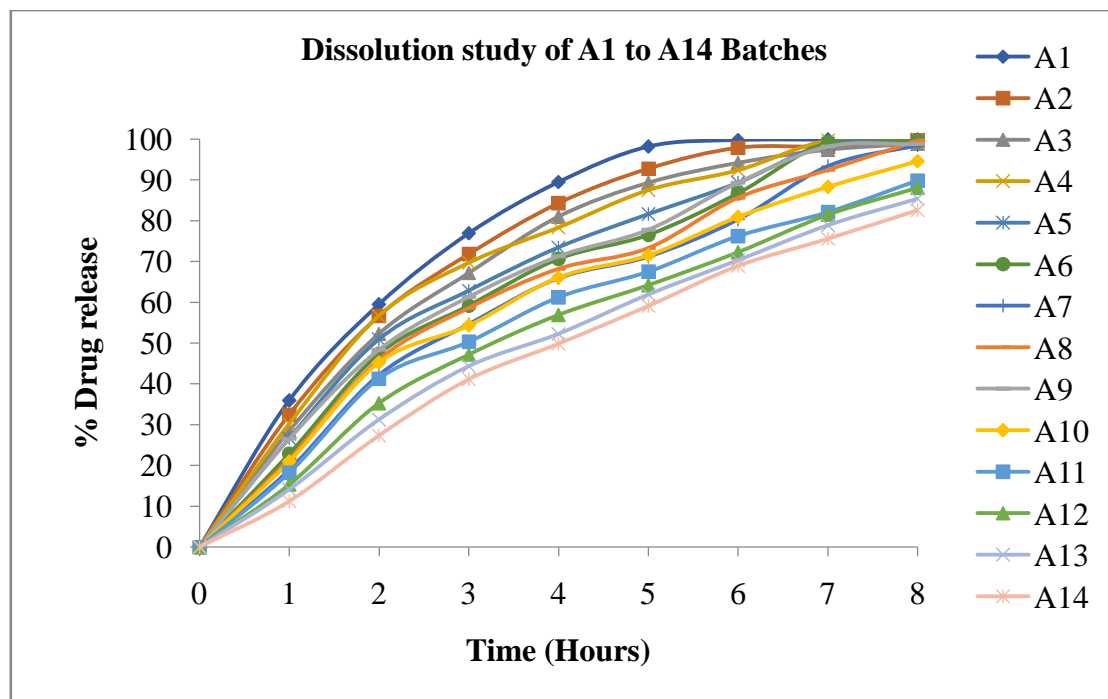
Figure 0.4 Dissolution study of A1 to A14 Batches

Based on the drug release data, it was observed that the A8 batch was the most satisfactory batch with respect to drug release and other parameters. Hence, the A8 batch selected as optimized batch and Stability study of the same batch initiated.

Drug release kinetic study

The drug release data was fitted in to different kinetic models. Among all, the best fitted model explained by Higuchi model because R^2 value of Higuchi model has 0.984.

Table 0.6 Kinetic modeling data

Batch No.	Zero order R2	First order R2	Higuchi R2	Kores Meyer R2	Kores Meyer Release exponent (n)
A1	0.9820	0.8500	0.9872	0.9826	0.4452
A2	0.9954	0.8786	0.9875	0.9960	0.4420
A3	0.9851	0.8532	0.9860	0.9858	0.4340
A4	0.9629	0.7885	0.9931	0.9719	0.4400
A5	0.9602	0.7858	0.9926	0.9709	0.4200
A6	0.9462	0.7887	0.9857	0.9696	0.4500
A7	0.9073	0.7807	0.9700	0.9700	0.4900
A8	0.9970	0.8817	0.9845	0.9857	0.4120
A9	0.9608	0.7892	0.9921	0.9716	0.4700
A10	0.9874	0.8325	0.9957	0.9886	0.4400
A11	0.9650	0.8305	0.9956	0.9878	0.4460
A12	0.9914	0.8505	0.9939	0.9929	0.4550
A13	0.9426	0.7997	0.9860	0.9741	0.4440
A14	0.9820	0.8712	0.9855	0.9975	0.4100

Higuchi model was found to best describe the R^2 (coefficient of determination). Korsmeyer-Peppas equation also best suits the dissolution data where the values of "n" were 0.45-0.89 indicating anomalous, non-Fickian, or nearly zero-order release mechanism. Drug release mechanism from prepared floating tablets of A8 batch was elucidated by fitting the in vitro dissolution data in Korsmeyer-Peppas equation. The value of "n" for the optimized formulation was greater than 0.45 indicating non-Fickian case II transport mechanism.

Stability Study

Stability study of optimized batch A8 performed for 1 month at 40 °C/75 % RH and evaluated for various parameters. Resulted parameters are tabulated below;

Table 0.7 Results of Stability Study of A8

Time	Appearance	% Drug Content	% Drug release in 8 hr
Initial	Complies	99.2 ± 3.1	99.7± 1.8
After 1 month	Complies	99.0 ± 3.5	99.2 ± 2.1

From the stability study data, it revealed that the formulation A8 stable at 40 °C/75 % RH condition. Results are well within acceptable limits.

CONCLUSION

The aim of the present investigation was to develop and evaluate transdermal patch of Itraconazole. Formulation development of Itraconazole Transdermal patch was initiated using Eudragit S 100 and HPMC E50 LV as matrix controlling polymer for matrix type Transdermal Patch. PEG 400 was selected as Plasticizer. Glycerin was selected as permeability enhancer. Preformulation study was performed to check the drug excipient compatibility. The IR spectra of Drug and final formulation found satisfactory. There is no any interaction between drug and excipients.

Further the linearity curve was developed in UV for method of analysis. Trials A1-A14 was initiated using different concentration of polymers in the formulation. The prepared patches were transparent and smooth in surface. The weight variation was found well within acceptable range. The thickness of patches was found uniform in nature and the variation is found satisfactory. Further, the surface pH of the patches was found between 6.8 to 7.1 and it is acceptable. The drug content, folding endurance and % elongation results of A1-A14 batches were found well within acceptable range. Initially the trial batches were taken with a single polymer like HPMC and Eudragit S100. The drug release was not achieved as per the target drug release profile for 8 hours. Hence the combination of these two polymers is taken and found better results than the single polymers. Based on the drug release data, it was observed that the A8 batch was the most satisfactory batch with respect to drug release and other parameters. Hence, the A8 batch selected as optimized batch and Stability study of the same batch initiated.

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