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FORMULATION AND EVALUATION OF TIOCONAZOLE TRANSDERMAL PATCHES

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ABSTRACT

The present research work is an attempt to formulate and evaluate Tioconazole Transdermal Patches for patient compliance by avoiding its gastrointestinal side effects. Tioconazole is an antifungal medication. It belongs to the Imidazole class. It is used to treat infections caused by a fungus or yeast. They are available in one-day doses, as opposed to the 7-day treatments commonly used in the past. Tioconazole is also used to treat ringworm, jock itch, athlete's foot, and tinea versicolor or sun fungus. Tioconazole taken orally undergoes a significant amount of metabolism. Glucuronide conjugates are the main metabolites. Erythema, stinging, blistering, peeling, edoema, prutitus, urticaria, burning and irritation of the skin, cramping, and urticaria are side effects of taking too much tioconazole. Tioconazole transdermal patches were prepared by solvent casting technique using various ratios of the polymers HPMC and PVP with the incorporation of PEG 400 as a plasticizer. Tioconazole transdermal patches were prepared using different ratios of HPMC and PVP polymers. Five formulations in total (TCZ1-TCZ5) were prepared. All the formulations were subjected to Physicochemical parameters such as Thickness, Uniformity of weight, tensile strength, folding endurance, percentage moisture absorption, percentage moisture loss and drug content. In vitro release studies of Tioconazole transdermal patches in phosphate buffer (pH, 7.4) were performed using a modified diffusion cell. Formulation TCZ3 containing HPMC and PVP in the ratio of 1:1 was found to be the most optimum formulation. TCZ3 was also found to exhibit a maximum in-vitro % drug release of about 92.54%. The patches were subjected to short term stability studies and were found stable.

KEYWORDS: Tioconazole, Transdermal patches, drug delivery system, HPMC, PVP, PropyleneGlycol.

1. INTRODUCTION

The oral route is currently the most prevalent method of medication delivery. While it has the notable benefit of being simple to administer, there are some significant disadvantages as well, including poor bioavailability due to hepatic metabolism (first pass) and the propensity to cause rapid blood level spikes, necessitating high and/or frequent dosing, which can be both expensive and inconvenient.[1] An improved method of drug delivery has been identified as a continuous intravenous infusion at a predetermined rate. This method avoids the hepatic first-pass elimination while also preserving a steady, long-lasting, and therapeutically effective drug level in the body. Both the benefits of a direct entrance of the medicine into the systemic circulation and circulating drug levels can be achieved with a carefully controlled intravenous infusion. However, because of the hazards associated with this method of drug delivery, patients must be admitted to hospitals and the medication must be closely monitored by doctors. There is a growing understanding that continuous transdermal drug administration through intact skin can closely mimic the advantages of intravenous drug infusion without any of its potential risks. The development of medicinal plasters in China and Japan shows that the potential of employing intact skin as a port of drug administration has long been understood. This sparked the interest of various biomedical scientists, who began to investigate the viability of transdermal medication administration.[2]

Transdermal drug, delivery systems (TDDSs) are self-contained discrete dosage forms that, when applied to undamaged skin, distribute the drug(s) through the skin portal at a predetermined and predictable rate into the systemic circulation over a protracted period of time.[3]

Based on the intended site of action of the medications they include, formulations for the skin can be divided into two groups. One causes localized skin effects, whereas the other causes systemic effects following drug uptake from the cutaneous microvascular network. Transdermal drug administration has advanced over the past 20 years from a clinical reality to the point where it can now be used as a reliable non-invasive diagnostic tool. Ensuring appropriate drug permeability through the stratum corneum. (SC) is ultimately the primary difficulty in developing a successful transdermal device However, interest in transdermal was rekindled in the current decade thanks to the introduction of various novel permeability

augmentation techniques. More than 20 transdermal patches on the market include 19 different pharmacological compounds.[4]

2. MATERIALS AND METHODS

2.1.Materials

Tioconazole was obtained as a gift sample from Yarrow Chemicals, Mumbai. Hydroxy propyl methylcellulose was purchased from Otto Chemika-Biochemika reagents, Mumbai. Poly vinyl pyrrolidone, PEG 400, Oleic acid and Glycerine was purchased from Karnataka Fine Chemicals, Bangalore. Chloroform was purchased from Sri Ram distributors, Mysuru. All other laboratory chemicals used in the study were of analytical reagents grade.

2.2.Methods

2.2.1.Preformulation studiesOrganoleptic properties[5]

The drug's colour, odour and taste were characterized and recorded using descriptive technologies.

Determination of melting point[6]

A small amount of the tioconazole drug was placed in a capillary tube that was closed at one end to measure the drug's melting point. The melting point device was used to position the capillary tube, and the temperature at which the medication melted was noted.

Solubility analysis[7]

Tioconazole's solubility will be tested in various solvents, including water, methanol, ethanol, chloroform and ethyl acetate.

Calibration curve of tioconazole[8]

50 mg of the drug, which was precisely weighed, was diluted in 50 ml of methanol to make a 1000 µg/ml solution. Using a Shimadzu UV-2450, the UV spectrum between 200 and 800 nm was recorded. The Maximum absorption wavelength (λ max) was identified. For the standard curve, Standard solutions having concentrations of 5, 10, 15, 20 and 25 µg/mL in methanol were prepared from a stock solution. The absorbance of these standards was observed at240 nm by a UV-visible spectrophotometer.

Drug-excipient compatibility studies by FTIR[9]

The drug-polymer and polymer-polymer interactions were studied by FTIR spectrometer. A total of 100 mg of dry potassium bromide powder was added after the drug and polymer had

been thoroughly pulverized and blended. A mortar and pestle are useful for mixing and grinding. The mixture is then placed under high pressure in an evacuable die to press it into a clear disc. A less complicated tool, like a hydraulic press, can frequently be used to create suitable KBr discs or pellets. Using dried KBr, the baseline correction was completed. Then, a dried drug and potassium bromide mixture spectra were scanned from 2000 cm^{-1} to 400 cm^{-1}.

Differential scanning colorimetry[10]

DSC studies of pure Tioconazole were carried out. In a DSC aluminum cup, precisely weighted samples were carefully introduced, and a heating curve was recorded in the temperature range of 40–280 °C at a heating rate of 10°C/min in an inert atmosphere.

2.2.2.Formulation of transdermal patches of tioconazole[11]

Tioconazole transdermal patches were prepared using the solvent casting technique. As per the composition shown in Table 1. The polymeric solution prepared using PVP and HPMC was dissolved in chloroform. For each formulation, the polymer ratio was changed while maintaining the overall weight constant at 180 mg. PEG 400 was added as a plasticizer. Under slow stirring with a magnetic stirrer, the Tioconazole drug was dissolved in polymer solution over 10 mins and poured into glass Petri plates. An inverted funnel was placed over Petri plates to control the Rate of drying and that was kept aside at room temperature overnight.

Table 1: Composition of transdermal patches of tioconazole.

Ingredients	Formulation code				
	TCZ 1	TCZ 2	TCZ 3	TCZ 4	TCZ 5
Tioconazole (mg)	50	50	50	50	50
PVP (mg)	50	65	80	115	130
HPMC (mg)	130	115	80	65	50
PEG 400 (ml)	2	2	2	2	2
Oleic acid (ml)	1	1	1	1	1
Chloroform (ml)	10	10	10	10	10

2.2.3.Evaluation of transdermal patches of tioconazole physical appearance[12]

The colour, clarity, flexibility, and smoothness of each prepared transdermal patch were evaluated.

Thickness of the patch[13]

Using a screw gauge, three distinct patch thicknesses were measured, and mean values were calculated.

Weight uniformity[14]

The patches measuring 1 × 1 cm^2 were cut and weighed using an electronic balance. The average weight was calculated and recorded.

Tensile strength[15]

Using a Universal Strength Testing Machine, the tensile strength of the patches was assessed. The device had a 1-gram sensitivity. There were two load cell grips in it. The upper one could be moved, but the lower one was fixed. A test film (4 x 1 cm^2) was placed between these cell grips, and force was gradually applied until the film broke. The kilogram dial reading was used to determine the film's tensile strength. Tensile strength is expressed as follows

$$\text{Tensile Strength} = \frac{\text{Tensile load at break}}{\text{Cross sectional area}}$$

Percentage elongation break test: The percentage elongation break was determined by noting the length just before the break point, the percentage elongation was determined from the below mentioned formula.

$$\text{Elongation percentage} = \left[\frac{(L_1 - L_2)}{L_2}\right] \times 100$$

Where L_1 is the final length of each strip, and L_2 is the initial length of each strip.

Folding endurance[16]

This was identified by repeatedly folding one film until it broke in the same spot. The value of folding endurance was determined by how many times the film could be folded in the same location without breaking.

Percentage moisture absorption[17]

The patches were precisely weighed and put in a desiccator with a saturated potassium chloride solution that was kept at room temperature to maintain a humidity state of 80–90% RH. The patches were stored until a steady weight was reached, then they were taken out and weighed. The difference between the final and original weights with regard to the initial weight was used to compute the percentage of moisture uptake.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss[18]

The patches were weighed separately and stored at room temperature in a desiccator containing anhydrous calcium chloride. When there was no change in the individual patch's weight, the final weight was recorded. The difference between the initial and final weights compared to the initial weight was used to compute the percentage of moisture loss.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug content[19]

The patch of size 1 cm^2 was cut and placed in a 50 ml volumetric flask, dispersed in 10 ml phosphate buffer (pH 7.4), stirred for 4 hrs and kept aside overnight to extract the drug from the patches. The absorbance of the solution was measured against the corresponding blank solution at 240 nm using a UV-Visible spectrophotometer. The experiment was repeated five times to validate the result.

***In vitro* release studies**

Procedure for *in vitro* release studies[20]

The fabricated patch was cut into 5cm^2 (2x2.5) and placed on the diffusion membrane/barrier membrane (regenerated cellulose which was permeable to low molecular weight substances), soaked overnight in distilled water and tied to a cylindrical cell open at both ends, such that the cell's drug releasing surface towards the receptor compartment which was filled with 50 ml of phosphate buffer solution of pH 7.4 at 32±1°C. The elution medium was stirred magnetically. The aliquots were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analysed for drug content using UV spectrophotometer at 240 nm.

3. RESULTS AND DISCUSSION

3.1.Preformulation studies organoleptic properties

The colour, odour and taste of the drug were characterized and recorded using descriptive terminology; the results are shown below:

Table 2: Organoleptic properties of tioconazole.

Sl. No.	Parameter	Observation
1	Colour	White
2	Odour	Odourless
3	Taste	Tasteless
4	Appearance	Whitish powder

Melting point of tioconazole

The reported melting point of tioconazole was found by the capillary technique to be 165-172˚C.

Solubility analysis[15]

Table 3: Solubility data of tioconazole.

Sl. No.	Solvent	Solubility
01.	Methanol	Very soluble
02.	Ethanol	Very soluble
03.	Ethyl acetate	Soluble
04.	Chloroform	Soluble
05.	Water	Very slightly soluble

The solubility studies of the Tioconazole drug revealed that the Tioconazole was very slightly soluble in water and soluble in methanol, ethanol, ethyl acetate and chloroform.

Calibration curve of tioconazole

The wavelength of maximum absorption (λ max) in methanol was found to be 240 nm.

Table 4: Data for calibration curve of tioconazole in methanol.

Sl. No.	Concentration (µg/ml)	Absorbance(λ =240)
01.	0	0
02.	5	0.202
03.	10	0.345
04.	15	0.503
05.	20	0.662
06.	25	0.793

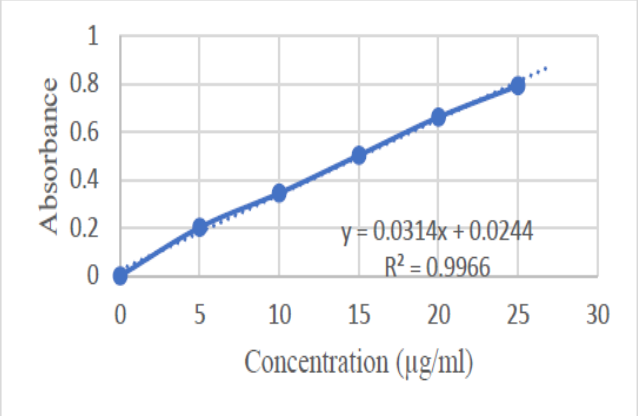

Figure 5: Calibration curve of tioconazole.

The maximum absorption (λ max) of Tioconazole in methanol was found to be 240 nm. The calibration curve was constructed by taking concentration on the x-axis and absorbance on the y-axis as shown in Fig. 1. Linear relationships were observed between concentration versus absorbance of Tioconazole supported by slope value as y = 0.0314x + 0.0244 and value of correlation coefficient as r^2 = 0.9966 close to unity. The data is represented in Table 4 and Figure 5.

Drug-excipient compatibility studies by FTIR

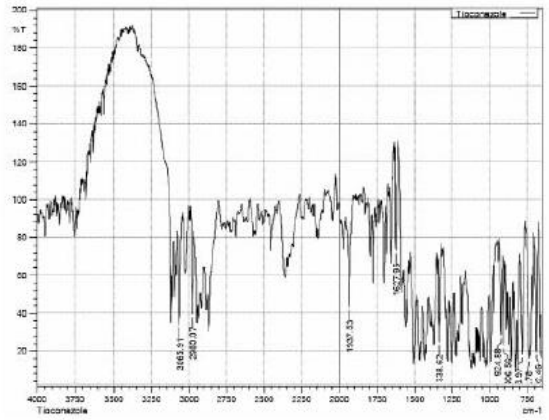

Figure 6: FTIR Spectrum of tioconazole.

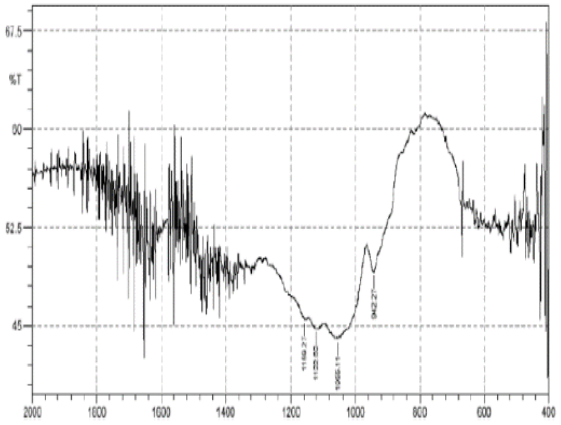

Figure 7: FTIR Spectrum of HPMC.

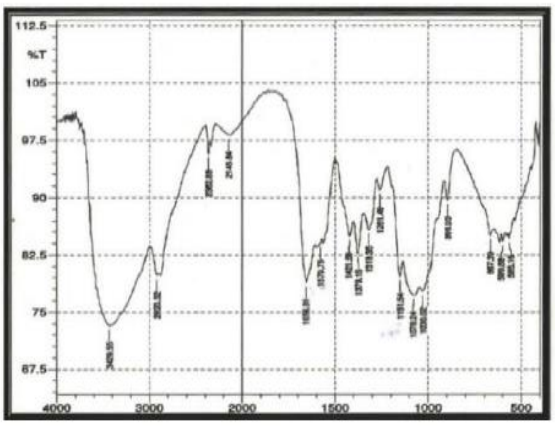

Figure 8: FTIR Spectrum of PVP.

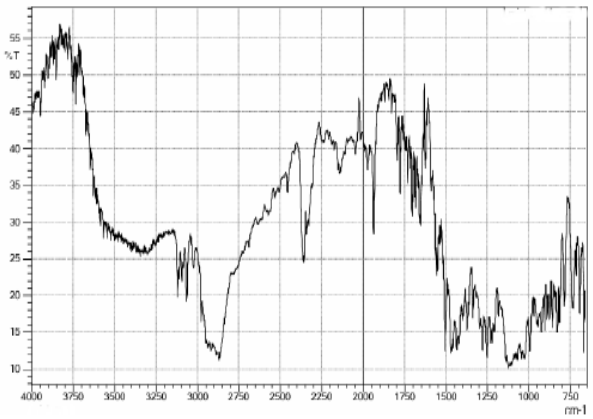

Figure 9: FTIR spectrum of physical Mixture of Tioconazole.

Table 5: FTIR Peaks of Tioconazole.

ReferencePeaks (cm^{-1})	Obtained peaks (cm^{-1})	Functionalgroups
1675-1600	1627.95	C=C
1470-1430	1470.85	C-H
1335-1250	1290.28	C-N
1450-1300	1340.62	C=C
750-650	737.78	C-S
800-600	692.46	C-Cl

Table 6: Comparative FTIR spectral data of drug and excipients.

Obtained peaks (cm^{-1})of drug	Obtained peaks (cm^{-1}) of physical mixture	Functional groups
1627.95	1628.38	C=C
1470.85	1469.90	C-H
1290.28	1289.89	C-N
1340.62	1341.11	C=C
737.78	736.97	C-S
692.46	693.55	C-Cl

The peaks show the Tioconazole characteristic peaks, indicating that the substance is Tioconazole. Both the pure drug Tioconazole's FTIR spectra and the physical mixture of Tioconazole samples are shown in Figures 6 and 9 respectively. The physical mixture peaks of the drug Tioconazole are identical when compared to the IR spectra of the drug (Tioconazole), indicating no interaction between the drug and polymers.

Differential scanning colorimetry of tioconazole

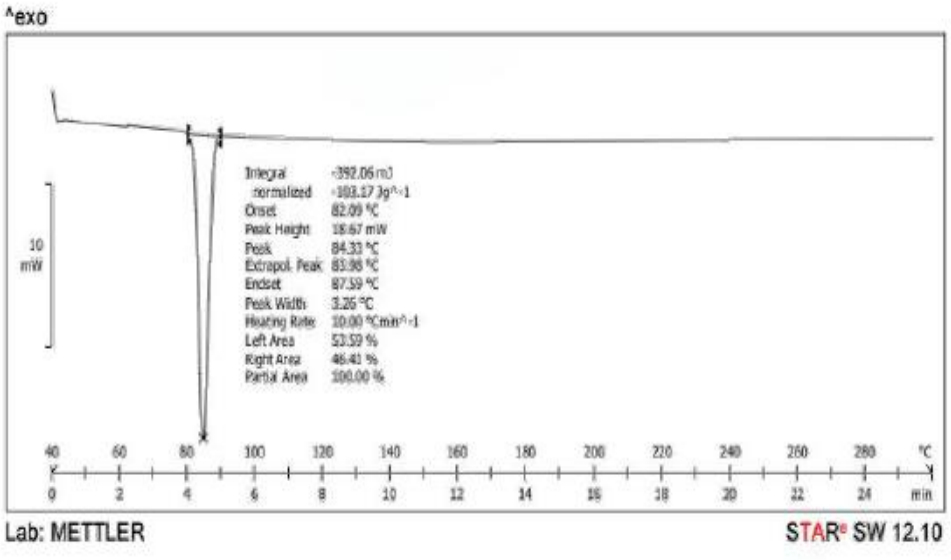

Figure 10: Differential scanning colorimetry of tioconazole.

The purity of the drug was verified by comparing the differential scanning calorimetry spectrum of the standard drug with that of the Tioconazole drug. Studied differential scanning calorimetry revealed a clear endothermic peak for tioconazole at 84.33 °C, which was also shown in the thermograms of the physical mixture, indicating no interaction between the drug and polymers.

3.2.Evaluation of transdermal patches of tioconazolephysical appearance

The formulated patches were found to be clear, smooth, uniform, flexible in their physical appearance and free from entrapment of air bubbles.

Table 7: Thickness uniformity, Weight uniformity, Tensile Strength and Percentage elongation data of Tioconazole TDDS.

Sl. No.	Formulation code	Thickness Mean ± S.D. (mm)	Weight uniformity Mean ± S.D. (mg)	Tensile strength (kg/cm^2) (Mean ± S.D) *	Percentage elongation (Mean ± S.D) *
01.	TCZ1	0.19±0.006	8.56±0.21	0.38 ± 0.015	41.2 ± 0.015
02.	TCZ2	0.16±0.006	8.3±0.1	0.53 ± 0.011	39.2 ± 0.013
03.	TCZ3	0.17±0.01	8.33±0.31	0.46 ± 0.012	38.8 ± 0.014
04.	TCZ4	0.20±0.006	8.43±0.31	0.45 ± 0.014	40.2 ± 0.013
05.	TCZ5	0.19±0.01	8.66±0.25	0.58 ± 0.015	39.6 ± 0.017

The thickness of the prepared patches varied in the range of 0.16±0.006 – 0.20±0.006 mm for various batches of prepared patches with low SD values implying uniformity of thickness (Table: 7).

Weight uniformity data have been recorded in Table: 7. The average weight of patches, range 8.3±0.1 - 8.66±0.25 mg with low SD values ensures compliance with uniformity of weight. The mean value was found to vary between 0.38 ± 0.015 to 0.58 ± 0.015 kg/cm^2.

The tensile strength results indicate the strength of the film and the risk of film cracking. But, no sign of cracking in prepared transdermal films was observed, which might be attributed to the addition of the plasticizer. The results of tensile strength are shown in Table 7.

The patches have shown moderate percentage elongation and were found satisfactory. The order of percentage elongation of the patch was as follows:

TCZ1>TCZ4>TCZ 5>TCZ 2>TCZ3

Folding endurance values varied between 52±1 to 111.66±3.5 (Table:8). The formulated film TCZ 5 exhibited optimal folding endurance (115) without any batch variation.

Study on moisture absorption that was done in desiccators. Every patch had the lowest proportion of moisture absorption. The data is shown in Table 8 and the order of the percentage moisture absorption is TCZ2>TCZ4>TCZ1>TCZ5>TCZ3. Low moisture uptake of the formulations may have reduced bulk and prevented them from microbial contamination.

The studies on moisture loss were conducted between 80 - 90% relative humidity. All of the patches had the lowest percentage of moisture loss. The data is shown in Table 8, with the percentage moisture loss occurring in the following order TCZ5>TCZ2>TCZ3>TCZ 4>TCZ1. The formulation's low moisture content keeps them stable and prevents them from drying out completely and becoming a brittle film.

Data of Tioconazole estimation in transdermal patches by UV-visible spectrophotometer at 240 nm have been recorded in Table 8. The formulation's percentage drug content ranges from 96.9±0.2 to 98.3±0.2. Low SD values indicate significant batch variability and acceptability of the process used to create and test high-quality transdermal patches with uniform medication distribution.

Table 8: Folding endurance, Percentage moisture absorption, Percentage moisture loss and % of Drug content data of Tioconazole TDDS.

Sl. No.	Formulation code	Folding endurance Mean ± S.D.(mg)	% Moisture absorption	% Moisture loss	% of Drug content Mean ± S.D.*
01.	TCZ1	52±1	5.26±0.0014	4.44±0.0014	97.3±0.2
02.	TCZ2	67.33±2.5	6.81±0.0021	7.27±0.0028	97.8±0.3
03.	TCZ3	84.66±3.1	3.07±0.0014	7.23±0.0035	98.9±0.2
04.	TCZ4	97.66±2.5	5.35±0.0021	6.12±0.0021	97.1±0.3
05.	TCZ5	111.66±3.5	4.16±0.0014	10.52±0.0028	98.2±0.1

***In-vitro* release studies**

Table 9: Percentage cumulative drug release.

Time (min)	% Cumulative Drug Release (Mean ± S.D.) *				
	Formulation Code				
	TCZ 1	TCZ 2	TCZ 3	TCZ 4	TCZ 5
0	0	0	0	0	0
15	10.37±0.117	18.67±0.524	13.41±0.295	15.67±0.276	11.91±0.335
30	16.70±0.322	26.55±0.435	22.54±0.43	19.47±0.339	17.78±0.659
60	36.62±0.221	43.58±0.39	40.68±0.393	37.54±0.43	33.46±0.558

120	48.71±0.43	56.56±1.368	54.57±0.37	45.48±0.433	48.15±0.854
240	55.49±0.669	64.75±0.433	69.82±0.513	54.28±0.324	51.29±0.454
360	63.22±0.214	70.03±1.496	78.23±0.854	68.25±0.237	65.92±0.781
480	85.32±0.743	79.72±0.0451	85.85±0.825	73.48±0.117	78.53±0.393
600	87.45±0.439	83.05±0.875	90.36±0.953	78.13±0.322	82.05±0.276
720	89.23±0.781	85.42±0.238	92.54±0.471	80.20±0.669	83.92±0.435

*** All values represent the mean of 3 readings (n-3)**

The cumulative percentage of the drug released in 24 h was found between 80.20±0.669% (TCZ 4) to 92.54±0.471 % (TCZ 3) for transdermal films. The percentage of drug release orders was as follows: TCZ3>TCZ1>TCZ2>TCZ5>TCZ4.

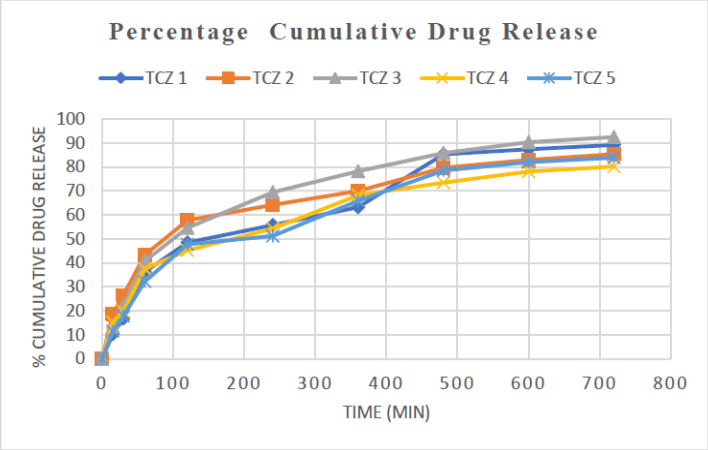

Figure 11: Cumulative percentage drug release curve.

The formulation TCZ3 showed a better *in-vitro* drug release profile across the cellulose membrane when compared to the other formulations. This might be attributed to the nature of polymers, plasticizers and even the permeation enhancer used. Thus, formulation TCZ3 is considered an optimized formulation. The results are depicted in Table 9.

4. CONCLUSION

Tioconazole transdermal patches were prepared by solvent casting technique with the incorporation of PEG 400 as a plasticizer. The prepared transdermal drug delivery system of Tioconazole using different ratios of polymers such as HPMC and PVP had shown good promising results for all the evaluated parameters. Based on the *In-vitro* drug release and drug content Result, formulation TCZ3 was concluded as an optimized formulation, which shows its higher percentage of drug release.

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