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Formulation and evaluation of transdermal patches of an Antifungal drug

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Abstract
Background: Bioavailability of Terbinafine HCl tablets as a result of the first-pass metabolism is approximately 40%.A single oral dose of 250mg Terbinafine results in a peak plasma concentration (C_{max}) of 0.83µg/ml within 2h of administration. The absorption of half-life is 0.8h and the distribution half- life is 4.6 h. This Originates the Transdermal drug delivery as an alternative route of administration for such drugs which can bypass the hepatic first-pass metabolism.
Objective: The objective of the present study was to compare the release effect of Terbinafine HCl from different polymeric (natural and synthetic) patches prepared using different permeation enhancers (natural and synthetic) and varying concentrations. The best polymer and permeation enhancer was selected based on the release of the drug from the patches.
Materials and Methods: Polymers such as HPMC, Chitosan, and Glycerin was used as a plasticizer. Enhancers used were Eucalyptus oil and Dimethyl Sulfoxide. Transdermal patches were prepared by using the solvent casting technique. FTIR was studied to estimate the incompatibility. Patches were evaluated for physicochemical Characteristics like thickness, weight variation, folding endurance, moisture loss, moisture absorption, drug content, and *In-vitro* diffusion studies.
Results: The results obtained showed no physical-chemical incompatibility between the drug and the polymers. HPMC was found to be a suitable polymer compared to Chitosan in preparation of transdermal patches. From the evaluation of patches, DMSO appears acceptable permeation enhancer compared to Eucalyptus oil as a natural origin. F19 containing 20% of DMSO was considered as the best formulation for the transdermal delivery of TH.
Conclusion: Transdermal patches were successfully prepared for TH and their evaluation studies of each dosage form revealed that topically applied TH patch possess immense potential to control the release rate of medicament to improve the bioavailability as well as patient compliance.

Keywords: chitosan, glycerin, HPMC, permeation enhancers, transdermal drug delivery

Introduction

Transdermal drug delivery means the delivery of drugs across the skin and into the systemic circulation taking advantage of the relative accessibility of the skin, is altogether different from topical drug delivery which can only target the locally affected areas The thorough understanding of the morphological, biophysical and physicochemical structure and properties of the skin is immensely important to deliver therapeutic agents through the human skin for systemic and desired effects [1].

The Transdermal drug delivery system has been in existence for a long time. The occurrence of systemic side effects with some of these formulations is indicative of absorption through the skin. Several drugs have been applied to the skin for systemic treatment. 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 [2]. The advantages of transdermal drug delivery include its ease of use, patient compliance, sustained drug delivery, local application, and safety. Oral medications must pass through the gastrointestinal tract, into the liver-where drugs are broken down, possibly lowering their effectiveness. With the transdermal patch, drugs enter directly into the bloodstream, reducing the risk of gastrointestinal side effects and bypassing breakdown by the liver [3].

Transdermal drug delivery systems are used to treat several diseases but with limitations due to poor penetration through the skin. The goal of improving the penetration of certain drugs via the transdermal route can be achieved through penetration enhancers [4].

Different methods and approaches have been used to alter the barrier properties of the skin in formulating drugs for transdermal delivery. One of the long-standing methods is by adding permeation enhancers of natural and synthetic compounds in the formulation. Permeation enhancers (PE) are substances that act to promote drug movement across the skin barrier and have various mechanisms of enhancement [5].

The fungus a crude organism and the fungi can live all over in the air, in the soil, on the plant, and in the Fungal infection, the classed by capable of causing harm fungi are very common to determine, and it not so serious if they are diagnosed fast and right treated. All the same, while fungal infections are solicitude, one of treated gain injection can easily fall out, as fungi can create problems to skill. The fungal are frequently present in the totality of surrounding conditions [6].

The most common fungal skin infections are dermatophytes, Pityriasis Versicolor, and Candidiasis. Approximately 90% of fungal skin infections are caused by ‘dermatophytes’, which are

parasitic fungi affecting the skin, hair, nails.[7] One of the leading antifungal agents for the treatment of fungal infections is Terbinafine HCl.[8] Terbinafine is an allylamine antifungal agent widely utilized in the treatment of infections caused by dermatophytes. It is also reported to have good activity *in vitro* against Cryptococcus, some species of Candida, Penicillinum marneffei, Aspergillus, and other filamentous fungi [9]. The mode of action for terbinafine involves inhibition of enzyme squalene epoxidase in fungal ergosterol biosynthesis, which induces accumulation of intracellular squalene and cell death [10].

Experimental

Material and Methods

Terbinafine was received as a gift sample from Medreich Pvt Ltd (Bangalore, India). Hydroxypropyl methylcellulose (HPMC) was a generous gift from Evonik India Pvt Ltd. (Mumbai, India). Chitosan was procured from Loba Chemie, Mumbai. Dimethyl sulfoxide (DMSO) was procured from Pyramid fine chem, Bangalore. Glycerin was procured from CDH laboratories, India. Other materials used in the study chloroform, methanol were of analytical grade. Double-distilled water was used throughout the study.

Preformulation Studies [11]

Before the formulation of a drug substance into a dosage form, it must be chemically and physically characterized. Pre-formulation studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

1. Organoleptic properties of Drug: [12]

The drug sample (Terbinafine Hcl) was noted for its organoleptic properties such as Color, odor, taste, and appearance.

2. Determination of melting point. [13]

The melting point of the sample was determined by the open capillary method. A small amount of powdered drug was filled inside the thin capillary tube and sealed from one side by melting. The capillary was placed into the melting point apparatus. After some time at a specific temperature, drugs were melted which was the melting point of the drug.

3. Determination of solubility. [14]

About 5mg Terbinafine hydrochloride was added to 10ml of various solvents and sonicated for 10minutes and inspected visually for solubility and compared with standard.

Determination of λ_{max} of Terbinafine Hcl [15]

Preparation of standard stock solution

Stock solution was prepared by dissolving 10mg of Terbinafine Hcl in 100ml distilled water in a volumetric flask, dissolved in 20 ml distilled water by shaking manually for 10 min. The volume was adjusted with the same up to the mark to give the final strength, i.e. 100µg/ml.

Selection of Wavelength for Analysis of Terbinafine Hydrochloride.

Appropriate volume 0.5ml of standard stock solution of terbinafine hydrochloride was transferred into a 10ml volumetric flask, diluted to a mark with distilled water to give concentration of 5µg/ml. The resulting solution was scanned in the UV range (200-400nm). In spectrum terbinafine hydrochloride showed absorbance maximum at 280nm.

Preparation of Dilution Samples & Calibration Curve of Terbinafine Hydrochloride.

Different aliquots of terbinafine hydrochloride in the range 0.5-3ml were transferred into series of 10ml volumetric flasks, and the volume was made up to the mark with distilled water to get concentrations 5, 10, 15, 20, 25, and 30µg/ml, respectively. The spectrum was recorded at 280nm. The calibration curve was plotted as concentration vs. absorbance.

Fourier transform infrared (FTIR) spectroscopy. [16]

Compatibility studies of the drug and the polymers were carried out using an FTIR spectrometer. 1 part of the sample is mixed thoroughly with 3 parts of dried potassium bromide and it was compressed into thin pellets. The pellets are then scanned under the IR region from 4000 cm^{-1} to 400cm^{-1}.

Preparation of Transdermal patches

- Transdermal patches were prepared by using the solvent casting method. Different ratios of polymers (HPMC and Chitosan) are accurately weighed and dissolved in chloroform, methanol (1:1) solution and kept aside to form a clear solution. The Drug was dissolved and mixed until a clear solution was obtained. To this solution Glycerin (20% v/v of polymer composition) and Permeation enhancers (DMSO, Eucalyptus oil) of different concentration was added and stirred.
- The Required quantity of the prepared solution was cast on a Petri dish lined with aluminum foil.
- A funnel of suitable size was inverted over the Petri dish.
- Casting solvent was then allowed to evaporate for 24h to obtain dry patches.
- After 24 hrs, the dried patches are taken out, wrapped in aluminum foil, packed in self-sealing covers, and stored in desiccators for further studies (evaluation).

Table 1: Formulation table of terbinafine HCl transdermal patches.

Formulation codes	Drug (mg)	HPMC (mg)	Chitosan (mg)	Eucalyptus Oil (%)	DMSO (%)	Glycerin (%)	Chloroform + Methanol(1:1)(ml)
F1(1:1)	100	100	-	-	-	20	10
F2(1:2)	100	200	-	-	-	20	10
F3(1:3)	100	300	-	-	-	20	10
F4(1:4)	100	400	-	-	-	20	10
F5(1:5)	100	500	-	-	-	20	10
F6(1:1)	100	-	100	-	-	20	10
F7(1:2)	100	-	200	-	-	20	10

F8(1:3)	100	-	300	-	-	20	10
F9(1:4)	100	-	400	-	-	20	10
F10(1:5)	100	-	500	-	-	20	10
F11 (1:3)	100	300	-	5%	-	20	10
F12 (1:3)	100	300	-	10%	-	20	10
F13 (1:3)	100	300	-	15%	-	20	10
F14 (1:3)	100	300	-	20%	-	20	10
F15 (1:3)	100	300	-	25%	-	20	10
F16 (1:3)	100	300	-	-	5%	20	10
F17 (1:3)	100	300	-	-	10%	20	10
F18 (1:3)	100	300	-	-	15%	20	10
F19 (1:3)	100	300	-	-	20%	20	10
F20 (1:3)	100	300	-	-	25%	20	10

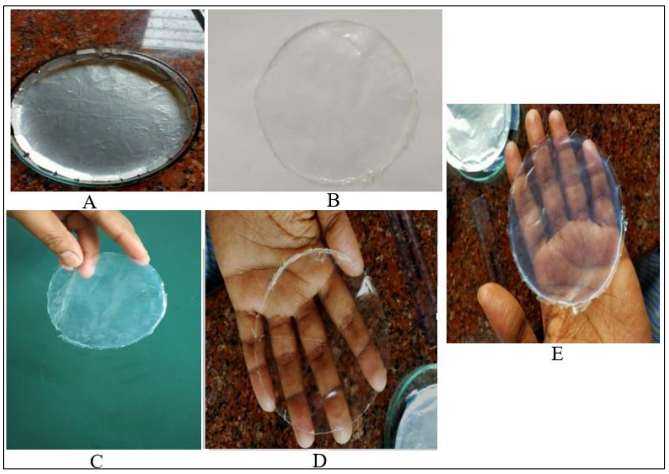

Fig 1

A. Formulation of Transdermal patches Using Solvent Casting Method.
B. Terbinafine Hcl Transdermal patch prepared with HPMC
C. Terbinafine Hcl Transdermal patch prepared with Chitosan
D. Terbinafine Hcl Transdermal patch prepared with HPMC and DMSO
E. Terbinafine Hcl Transdermal patch prepared with HPMC and Eucalyptus Oil

Evaluation of Transdermal patches

1. Physical appearance: [17]

All the prepared patches are visually inspected for color, clarity, flexibility and smoothness.

2. Thickness: [18]

The thickness uniformity of the transdermal patch was recorded at three different places using a vernier caliper and the average thickness was determined.

3. Weight Uniformity: [19, 20]

For each formulation, three randomly selected patches were used. For the weight Uniformity test, 3 patches from each batch were weighed individually and the average weight was calculated.

4. Folding Endurance: [21]

Evaluation of folding endurance involves determining the folding capacity of the patch subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the patch of a specific area (5×5 cm) at the same place until it breaks. The number of times the films could be folded at the same place without breaking is folding endurance value.

5. Percentage moisture absorption: [22]

The percent moisture absorption test was carried out to check the physical stability and integrity of the patch at high humid conditions. In the present study, the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the desiccators containing a 200ml saturated solution of potassium chloride, to get the humidity inside the desiccators at 84%RH. After 3days the patches were taken and weighed the percentage moisture absorption of the patch was found.

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

6. Percentage moisture loss: [23]

The patches were weighed accurately and kept in a desiccator containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture loss was calculated using the formula.

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

7. Water Vapour transmission rate (WVTR): [24]

Glass vials of 5ml capacity were filled with 1g of anhydrous calcium chloride and the polymer patches of 2.25cm^2 were fixed onto the brim. The assembly was accurately weighed and placed in a humidity chamber (80±5%) at 27±2°C for 24hours. The vials were removed and weighed at 24h time intervals to note down the weight gain.

$$\text{Water vapour Transmission rate} = \frac{\text{Final weight - Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

8. Drug content: [25]

The prepared drug contained patches specified surface area of 1cm^2 were cut and transferred into a graduated glass stopper flask containing 100ml of phosphate buffer 7.4. The flask was shaken for 4hrs on a mechanical shaker. Then the solution was filtered through 42number whatman filter paper and 1ml was diluted to 10ml with phosphate buffer and the absorbance was measured at 280nm using a placebo patch solution as blank and the drug content was calculated.

$$\%\ \text{Drug content} = \frac{\text{Actual weight of drug}}{\text{Theoretical weight of drug}} \times 100$$

9. *In vitro* diffusion studies: [26, 27].

In vitro, skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 50ml. The semi-permeable membrane-70 was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into a size of 1cm^2 and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50rpm; the temperature was maintained at 37±0.5°C. The samples of 1ml were withdrawn at a time interval of 30mins, 1, 2, 3, 4, 5, 6, and 24 hrs, analyzed for drug content spectrophotometrically at 280nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time.

Results and Discussion

Preformulation studies

Preformulation studies of Terbinafine Hydrochloride was carried based on the following parameters

1. Organoleptic properties of drug:

The drug was identified based on of Organoleptic properties. Terbinafine Hcl is an Off-white color; it is odorless, bitter in taste, and appeared as Fluffy powder.

2. The melting point of drug

The melting point range of the Terbinafine hydrochloride was found to be 197°C. The normal range of the melting point of Terbinafine Hcl is 195-197°C, which shows that the melting point of the drug was lying between the range. The melting point indicates the purity of the drug.

3. Solubility of drug

Terbinafine hydrochloride was freely soluble in anhydrous ethanol and methanol, slightly soluble in acetone, and very slightly soluble in water that shows it is lipophilic in nature.

Calibration Curve of Terbinafine Hydrochloride.

For the preparation of the calibration curve, samples were prepared from stock solution (5, 10, 15, 20, 25, 30 µg/ml). The absorbance of the sample was taken at 280nm. The Calibration curve of Terbinafine Hcl is presented in Figure No 2, and data are presented in Table No 2.

Table 2: Analytical data for calibration curve of Terbinafine Hydrochloride

SL no	Concentration(µg/ml)	Absorbance
1.	5	0.1281±0.0003
2.	10	0.2449±0.0005
3.	15	0.3412±0.0003
4.	20	0.4539±0.0006
5.	25	0.5485±0.0003
6.	30	0.6474±0.0003

The graph plotted between concentration and absorbance was found to be a linear and straight line.

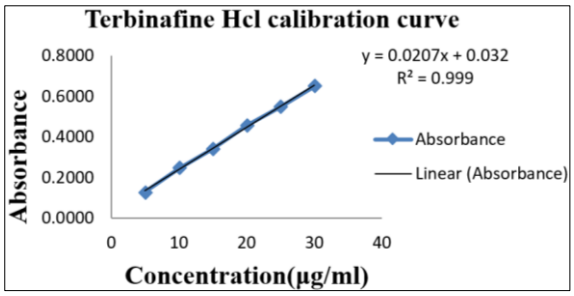

Fig 2: Calibration curve of Terbinafine Hcl.

Standard Curve Equation

$$y = 0.020x + 0.032 \; R^2=0.999$$

Fourier Transform Infrared (FTIR) Interaction Studies

Compatibility studies of the drug and the polymers were carried using Shimadzu–FTIR spectrometer. The Infrared (IR) spectra of Terbinafine Hcl and physical mixtures with Terbinafine Hcl, polymer (HPMC), and other excipients (DMSO, Eucalyptus oil) were recorded by FTIR spectrometer as shown in Fig No 3, 4 & 5. The spectra of Terbinafine Hydrochloride were shown to exhibit the peak at 3040.68 cm^{-1}: OH stretching, 1466.15 cm^{-1}: C-H bending, 1363.46 cm^{-1}: COOH stretching, 958.4 cm^{-1} for C-H bending, 775.86 cm^{-1} for C- Cl stretching vibrations. From the characteristic peak, it was observed that the chemical integrity of drug was not disturbed in both physical mixtures and polymer with other excipients (permeation enhancers). This proves that there is potential compatibility of drug and excipients.

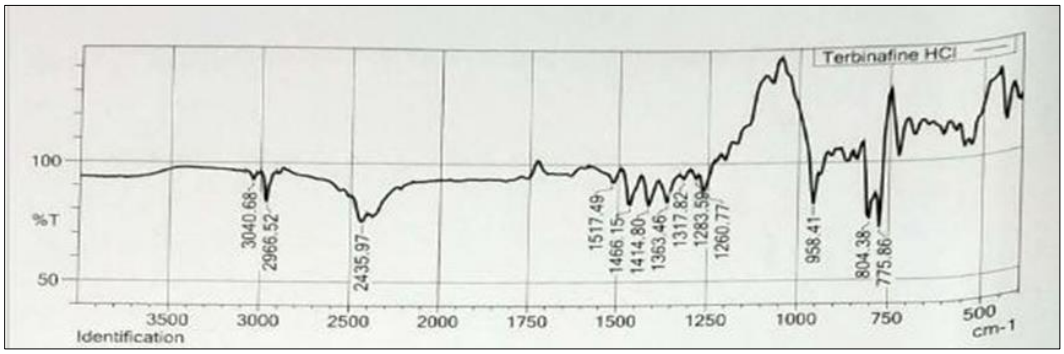

Fig 3: FTIR Spectra of Terbinafine Hcl

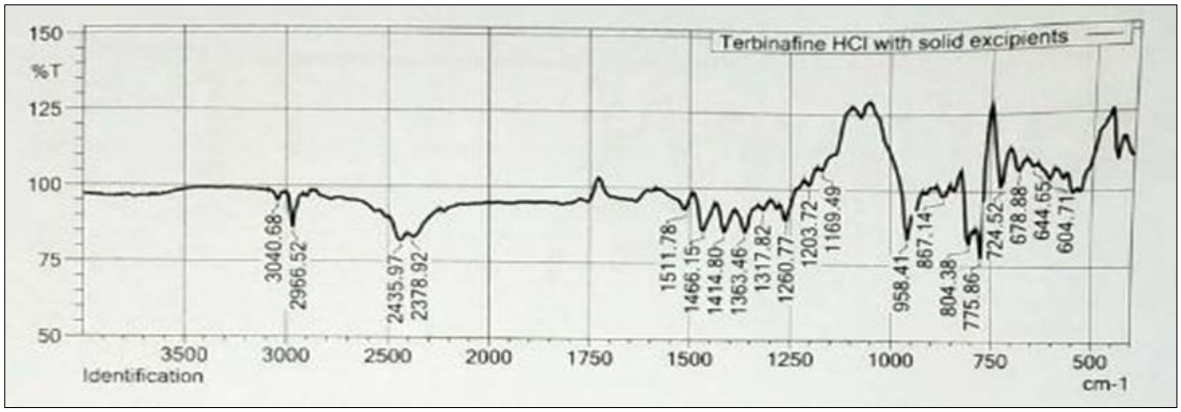

Fig 4: FTIR Spectra of Terbinafine Hcl+ HPMC+ Chitosan.

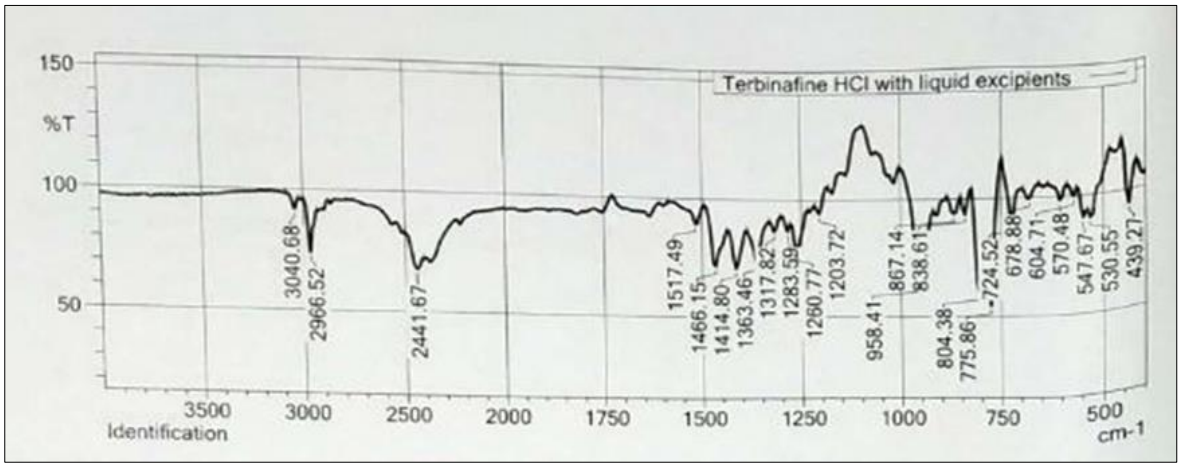

Fig 5: FTIR Spectra of Terbinafine Hcl+ HPMC+ Chitosan+ DMSO+ Eucalyptus oil.

Evaluation of Transdermal patches

Table 3: Physicochemical evaluation data of Terbinafine HCl transdermal patches

FR Code	Physical Appearance	*Thickness (mm)	*Weight uniformity (gm)	*Folding Endurance	*%Moisture Absorption	*%Moisture loss	*WVT (g/cm^2)	Drug content
F1	Transparent, Smooth, Uniform & Flexible	0.183±0.005	0.373±0.012	48±0.816	3.301±0.161	0.93±0.013	0.056±0.008	89.48±1.106
F2	Transparent, Smooth, Uniform & Flexible	0.187±0.011	0.387±0.025	43±1.247	3.318±0.135	1.90±0.020	0.042±0.002	92.55±1.441
F3	Transparent, Smooth, Uniform & Flexible	0.190±0.005	0.403±0.005	36±0.471	3.491±0.052	1.95±0.012	0.028±0.001	94.78±0.461
F4	Transparent, Smooth, Uniform & Flexible	0.193±0.008	0.417±0.012	39±0.471	3.535±0.227	1.44±0.016	0.056±0.005	93.39±0.372
F5	Transparent, Smooth, Uniform & Flexible	0.195±0.015	0.417±0.005	35±1.247	3.503±0.183	1.91±0.012	0.042±0.002	90.91±0.596
F6	Transparent, Smooth, Uniform & Flexible	0.170±0.008	0.250±0.033	41±1.247	3.600±0.025	2.44±0.012	0.060±0.002	72.18±0.037
F7	Transparent, Smooth, Uniform & Flexible	0.173±0.005	0.253±0.025	44±1.633	3.876±0.021	2.34±0.008	0.058±0.002	74.97±0.156
F8	Transparent, Smooth, Uniform & Flexible	0.183±0.008	0.327±0.033	39±2.867	4.015±0.013	2.68±0.020	0.064±0.003	75.97±0.824
F9	Transparent, Smooth, Uniform & Flexible	0.190±0.003	0.347±0.029	25±2.867	4.074±0.031	3.85±0.037	0.076±0.003	76.80±1.038
F10	Transparent, Smooth, Uniform & Flexible	0.197±0.005	0.373±0.031	30±2.449	4.380±0.045	3.10±0.021	0.083±0.002	79.84±0.954
F11	Transparent, Smooth, Uniform & Flexible	0.180±0.010	0.397±0.005	32±2.867	3.741±0.020	3.62±0.029	0.069±0.001	85.40±1.124

F12	Transparent, Smooth, Uniform & Flexible	0.190±0.005	0.403±0.009	35±2.449	3.792±0.024	2.26±0.021	0.083±0.003	87.32±0.738
F13	Transparent, Smooth, Uniform & Flexible	0.197±0.012	0.400±0.008	39±1.247	3.704±0.016	2.29±0.025	0.056±0.005	87.71±0.906
F14	Transparent, Smooth, Uniform & Flexible	0.193±0.004	0.397±0.005	36±1.633	3.765±0.025	2.24±0.029	0.097±0.001	88.77±1.002
F15	Transparent, Smooth, Uniform & Flexible	0.197±0.005	0.407±0.010	44±2.055	3.691±0.020	3.58±0.053	0.056±0.002	86.08±1.145
F16	Transparent, Smooth, Uniform & Flexible	0.183±0.009	0.392±0.005	35±2.055	3.346±0.029	1.41±0.028	0.042±0.002	86.07±1.064
F17	Transparent, Smooth, Uniform & Flexible	0.183±0.011	0.396±0.008	42±2.867	3.292±0.045	1.43±0.024	0.055±0.003	89.48±1.293
F18	Transparent, Smooth, Uniform & Flexible	0.187±0.008	0.397±0.010	39±2.055	3.319±0.033	1.40±0.029	0.040±0.002	90.80±0.916
F19	Transparent, Smooth, Uniform & Flexible	0.180±0.001	0.390±0.002	47±1.701	2.878±0.021	1.38±0.016	0.014±0.001	98.89±0.782
F20	Transparent, Smooth, Uniform & Flexible	0.190±0.007	0.398±0.006	41±2.449	3.255±0.020	1.44±0.033	0.028±0.003	92.26±0.822

*Indicates average of 3 values

Table 4: *In vitro* cumulative drug release of terbinafine HCl transdermal patches

Formulation code	Time(hrs)							
	0.5	1	2	3	4	5	6	24
F1(1:1)%	2	3	6.2	9.0	14.1	18.0	29.3	42.4
F2(1:2)%	3.4	4.3	12.3	19.0	25.0	24.8	30.7	57.7
F3(1:3)%	4.6	4.9	7.0	22.0	24.7	30.6	31.6	71.7
F4(1:4)%	5.8	14.1	16.6	22.9	25.7	31.0	33.4	59.8
F5(1:5)%	11.3	13.4	15.9	18.1	24.2	30.8	35.7	64.3
F6(1:1)%	1.7	2.6	3.6	4.5	5.9	9.4	12.8	15.2
F7(1:2)%	1.0	1.6	2.3	4.2	7.7	10.0	12.9	14.3
F8(1:3)%	1.8	2.9	5.9	6.2	7.2	8.7	10.3	23.2
F9(1:4)%	4.9	5.7	8.1	13.5	15.0	17.3	20.3	22.1
F10(1:5)%	1.3	4.4	7.0	9.5	16.8	18.9	26.2	25.0
F11 (1:3)%	7.9	15.0	17.4	22.9	29.5	36.7	40.4	67.1
F12 (1:3)%	7.0	15.2	17.1	19.9	27.7	35.7	39.8	69.0
F13 (1:3)%	7.6	13.0	20.5	25.9	32.3	36.6	40.5	69.2
F14 (1:3)%	7.9	16.2	18.1	26.3	34.4	36.3	40.7	69.6
F15 (1:3)%	7.5	15.0	18.5	25.4	33.0	37.4	41.1	71.7
F16 (1:3)%	12.5	17.8	21.9	29.0	33.0	38.0	42.4	78.8
F17 (1:3)%	13.2	16.4	20.3	25.0	32.0	35.2	49.9	79.3
F18 (1:3)%	11.4	15.8	17.6	25.5	28.4	32.4	46.5	85.6
F19 (1:3)%	10.6	13.5	19.3	23.9	29.0	33.3	48.8	91.3
F20 (1:3)%	9.8	12.5	17.3	21.9	24.4	29.8	45.1	89.0

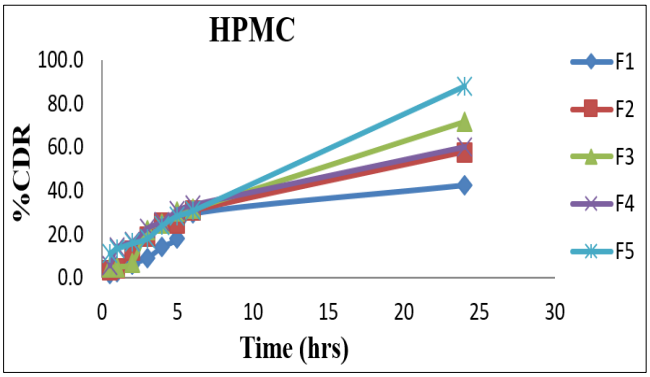

Fig 6: *In-vitro* drug release profile of formulation F1 to F5 using HPMC

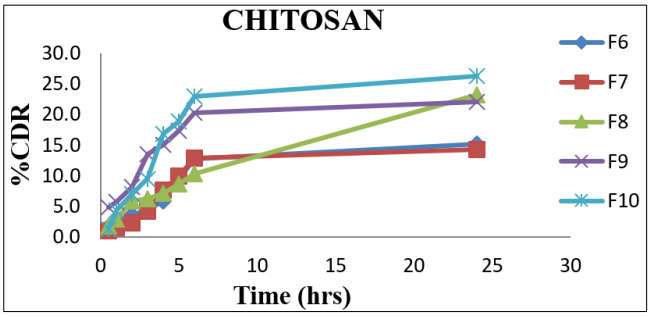

Fig 7: *In-vitro* drug release profile of formulation F6 to F10 using Chitosan

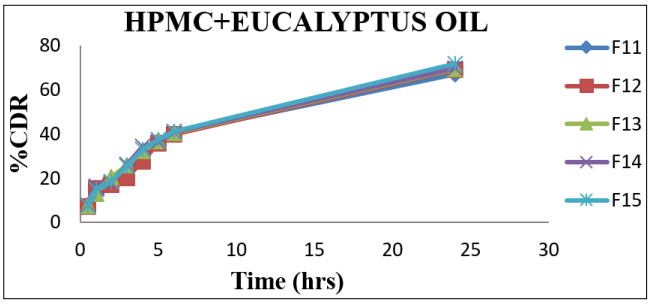

Fig 8: *In-vitro* drug release profile of formulation F11 to F15 using HPMC as polymer and Eucalyptus Oil as permeation enhancer.

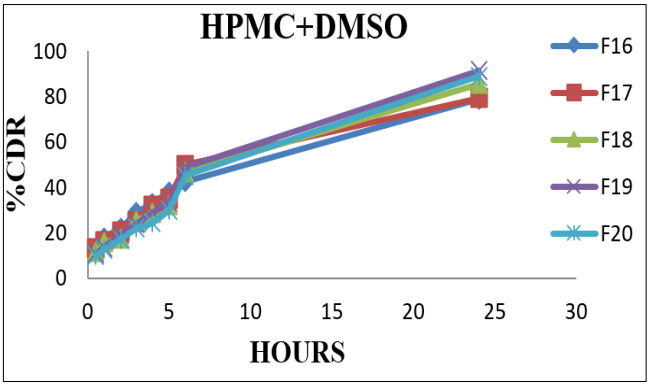

Fig 9: *In-vitro* drug release profile of formulation F16 to F20 using HPMC as polymer and DMSO as permeation enhancer.

A Total of 20 Terbinafine HCl formulations prepared from different polymeric (natural and synthetic) and permeation enhancers (natural and synthetic) in varying concentrations as shown in table 1. The results of thickness, Weight uniformity, folding endurance, %Moisture absorption, %Moisture loss, WVT, and %Drug content are shown in Table 3. In-vitro drug release results are shown in Tables 4.

1. Physical appearance

All the patches were evaluated for their physical appearance, and they were found to be transparent, smooth, uniform, and flexible.

1. Thickness

The thickness of the optimized patches was varied from 0.183±0.011mm to 0.195±0.005mm for HPMC, 0.170±0.008mm to 0.197±0.005 for Chitosan and 0.180±0.010 mm to 0.197±0.005 mm for Eucalyptus oil, 0.180±0.001mm to 0.190±0.007mm for DMSO. From these values, it was observed that the thickness of the polymer depends on the solubility and concentration of the polymer. As the solubility decreases and concentration increases would increase the thickness of the patch. It infers that usage of the competent polymer is the prerequisite step to prepare a patch of optimum thickness, which can retard the release of drugs from the patch. Low SD values in the patch ensure uniformity of the patches prepared by solvent casting technique.

2. Weight Uniformity

The Weights ranged between 0.373±0.012gm to 0.417±0.012 for HPMC patches, 0.250±0.033 gm to 0.373±0.031gm for Chitosan patches and 0.397±0.005gm to 0.407±0.010gm for Eucalyptus oil, 0.390±0.002gm to 0.398±0.006 for DMSO, which indicates that different batches patch weights, were relatively similar. Weights of DMSO patches are less compared to weights of Eucalyptus oil. There were no significant differences ($p>0.05$) in the weights of the patches within and among the batches while this was also the case with the patches thickness within the batches but not among the batches.

3. Folding Endurance:

Folding endurance was measured manually; patches were folded 48 times maximum in HPMC compared to Chitosan (41times). 32±2.867 to 44±2.055 number folds for Eucalyptus oil, 35±2.055 to 47±1.701 number folds for DMSO with slight variation among the patches. Folding endurance results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

The folding endurance was found to be best in the patches containing DMSO as a penetration enhancer.

4. Percentage moisture absorption:

Chitosan patches absorbed the highest amount of moisture (3.600±0.025-4.380±0.045) and HPMC patches absorb the least amount of moisture (3.301±0.161-3.535±0.183). Patches prepared from Eucalyptus oil absorbed the highest amount of Moisture ranged from 3.691±0.020% to 3.792±0.024%, DMSO patches absorb the least amount of moisture ranged from 3.255±0.020% to 3.346±0.029%. Low moisture absorption protects the patch from microbial contamination and bulkiness of the patches

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5. Percentage moisture loss

The highest amount of moisture loss was found in Chitosan (2.34±0.008-3.85±0.037) and the lowest moisture loss was found in HPMC (0.93±0.013-1.95±0.012). The percentage of moisture loss was found more in Eucalyptus oil patches ranged from 2.24±0.029% to 3.62±0.029%, lowest moisture loss was found in DMSO patches ranged from 1.38±0.016% to 1.44±0.033%. The moisture loss varied with different penetration enhancers. It was found that batches containing DMSO as penetration enhancers were best in terms of moisture loss since they had a minimum water loss. The less moisture loss in the formulations helps the patch to remain stable, brittle, and free from complete drying.

6. Water Vapour transmission rate (WVTR)

Water vapor transmission studies were carried out to determine the permeability characteristics of the transdermal patches. The water vapour transmission rates for the prepared patches were ranged from 0.028±0.001g/cm^2 to 0.056±0.008g/cm^2 24h for HPMC, 0.058±0.002001g/cm^2 to 0.083±0.002001**g**/cm^2 24h for Chitosan and 0.056±0.005g/cm^2 to 0.097±0.001 g/cm^2 24h for Eucalyptus oil patches, 0.014±0.001 g/cm^2 to 0.055±0.003 g/cm^2 24h for DMSO patches, indicating that all the formulations were permeable to water vapor. HPMC has less water vapor transmission rate compared to Chitosan. DMSO patches have less water vapor transmission rate compared to Eucalyptus oil patches. The low water vapor transmission rates again emphasize the stability aspects of long-term storage.

7. Drug Content

The drug content ranged from 89.48±1.106% to 94.78±0.46%1 for HPMC, 72.18±0.037% to 79.84±0.954% for Chitosan. Percentage drug content was found to be highest for HPMC patches when compared to Chitosan patches. Good uniformity of drug content among the batches observed with the formulations of DMSO patches ranged from 86.07±1.064% to 98.89±0.782%. Drug content for Eucalyptus oil patches was found to be 85.40±1.124% to 88.77±1.002. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability, which was determined using an ELICO spectrophotometer.

8. *In vitro* diffusion studies

The cumulative percentage release of Terbinafine Hcl from prepared transdermal patches was investigated for 24h, shown in Table 4. *In vitro* drug release at the end of 24 h for HPMC patches relationship can be established as F3>F5>F4>F2>F1. For Chitosan patches drug release from F6 to F10 was found to be F10>F8>F9>F6>F7 thus, by varying amounts of polymer in patches, percent release can be varied. Among five formulations i.e. F1, F2, F3, F4, F5 with different concentrations of HPMC, formulation F3 shows more drug release. Hence F3 (1:3) were selected for further permeation studies to which natural (Eucalyptus oil) and synthetic (DMSO) permeation enhancers were incorporated, and new formulations with permeation enhancers were labeled from F11 to F20. The cumulative percentage release of eucalyptus oil formulations from F11 to F15 was found in the range of 67.1% to71.7% for 24h. The order of drug release for patches of Eucalyptus oil was found to be F15>F14>F13>F12>F11. For DMSO formulations drug release

from F15 to F20 was found to be 78.8% to 91.3% for 24h.. The order of drug release for patches of DMSO was found to be F19>F20>F18>F17>F16. F19 containing 20% of DMSO was considered as the best formulation compared to Eucalyptus oil as natural origin. The *in-vitro* diffusion studies of various formulations were carried out to indicate the influence of permeation enhancers on the release of the drug. The cumulative amounts of drug released per square centimeter of patches were plotted against time were shown in Figures No 6, 7, 8 & 9.

Conclusion

The following conclusions were drawn from the results obtained;

- From the compatibility studies using FTIR Spectra, it was concluded that there was no interaction between polymer and drug hence they are compatible with each other and thus suitable for the formulation.
- Based on physicochemical characterization and drug release patterns of HPMC patches, HPMC was selected as the best polymer compared to Chitosan. Among five formulations F3 shows more drug release of 71.7% for 24hrs, %drug content was found to be 94.78%.
- F3 (1:3) were selected for further permeation studies to which natural (Eucalyptus oil) and synthetic (DMSO) permeation enhancers were incorporated.
- After performing all physicochemical characterization tests of the patches, it could be concluded that the polymeric patches formulated using DMSO as a synthetic penetration enhancer (DMSO) were excellent to retain and maintain drug content compared to natural penetration enhancer (Eucalyptus oil).
- Among five formulations with different concentrations of DMSO as a penetration enhancer, the best formulation was found to be F19 containing 20% of enhancer showed optimum drug release rate for 24h and extent of drug release was 91.3%, thickness (0.180mm), weight uniformity (0.390gm), folding endurance(47number), %moisture absorbed (2.878%), %moisture loss (1.38%), WVT (0.014gm/cm^2) and %drug content(98.89%).

Based on the observations, it can be concluded that the attempt of formulation and evaluation of Transdermal patches of an Antifungal drug was found to be successful in the release of the drug for an extended period of 24hrs.

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