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Formulation and *in-vitro* Evaluation of Terbinafine HCL Transdermal Patches

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Abstract
The present study transdermal patches of the Terbinafine Hcl were prepared using polymers like HPMC, SCMC and carbopol 934 with different concentration. These transdermal patches will be characterized for their physicochemical properties like thickness uniformity of patches from 0.211 ± 0.016 mm to 0.232 ± 0.013 mm, weight uniformity of patches between 0.312 ± 0.033 mg and 0.398 ± 0.021 mg, tensile strength of patches vary between 3.21 ± 0.114 to 4.62 ± 0.111 kg/mm^2, folding endurance of patches between 74.11 ± 4.231 to 97.56 ± 6.231, drug content uniformity, in vitro release studies. Different techniques, FTIR (Fourier Transform infra red) and DSC (differential scanning calorimetry) were used to estimate the incompatibility.

Keywords:
Terbinafine HCL, transdermal patches, HPMC, sodium carboxy methyl cellulose, carbomer 934, DSC, FTIR

INTRODUCTION

Transdermal drug delivery systems (TDDS) are adhesive drug containing devices of defined surface area that delivers predetermined amount of drug to the intact skin at a preprogrammed rate. The transdermal delivery has gained importance in recent years. The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa, and improved patient compliance. Some of the anti hypertensive drugs already have been formulated and evaluated as transdermal patches but most of them still been unexplored. Transdermal formulation of anti fungal drug is promising aspect in near future. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time [1-3]. TDDS has gained a lot of interest during the last decade as it offers many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, less frequency of administration, reduction in gastrointestinal side effects and improves patient compliance[4]. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin[5].

Most treatments are either systemic antifungal medications, such as Terbinafine and itraconazole, or topical, such as nail paints containing ciclopirox or amorolfine. There is evidence that combining systemic and topical treatments is beneficial[6]. For superficial white onychomycosis, systemic rather than topical antifungal therapy is advised[7].

MATERIAL AND METHOD

Material

Terbinafine-HCL was received as a gift samples from Systopic Laboratories, New Delhi, India. Hydroxypropyl methylcellulose (HPMC) and sodium carboxy methyl cellulose (SCMC) and carbopol 934 were procured from Merk, Mumbai, India, respectively. Glycerol was procured from S.D Fine chemical Ltd. (Mumbai, India). All other laboratory chemicals used in the study were of analytical reagents grade. Double distilled water was used throughout the study.

Method

Preparation of Transdermal patches

Different formulation were prepared with various ratio of (HPMC: carbomer), (SCMC: carbomer), (HPMC: SCMC), (HPMC: SCMC: carbomer) .Many experiments were conducted by varying the concentrations of those polymers in order to identify the optimum concentration required for polymer solution.

Step I: Required quantity of HPMC, SCMC and carbomer 934 was soaked in sufficient quantity of distilled water and kept overnight for swelling.

Step II: The polymer solutions were mixed with magnetic stirrer, until a uniform solution was obtained.

Step III: An appropriate amount of Terbinafine HCL was solubilized in above polymer solution with continuous stirring until an uniform solution obtained.

Step IV: Then the polymer solutions was poured in to a petridish on level surface and allowed to evaporate at controlled rate by covering the petridish with funnel to avoid blistering effect after drying of patches.

EVALUATION OF TRANSDERMAL PATCHES

Physical appearance

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

Thickness uniformity

The thickness of the formulated film was measured at 3 different points using a digital caliper and average thickness of three reading was calculated [8,9].

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 3 patches from each batch were weighed individually and the average weight was calculated [9,10].

Folding endurance

The folding endurance was measured manually for the prepared patches[11,12]. A strip of film (5 x 5 cm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

Percentage moisture absorption

The patches were weighed accurately and placed in the desiccators containing 100 mL of saturated solution of potassium chloride, which maintains 80-90% RH[13]. After 3 days, the patches were taken out and weighed. The study was performed at room temperature.

The percentage moisture absorption was calculated using the formula:

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

Percentage moisture loss

The patches were weighed accurately and kept in a desiccators containing anhydrous calcium chloride[14]. After 3 days, the patches were taken out and weighed. The moisture loss was calculated using the formula:

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

Water vapour transmission rate

Glass vials of 5 mL capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymer patches of 2.25 cm2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 h[14,15]. The vials were removed and weighed at 24 h time intervals to note down the weight gain.

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

Tensile strength

Tensile strength of the film was determined with Universal strength testing machine (Hounsfield, Slinfold, Horsham, U.K.). The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size ($4 \times 1 cm^2$) was fixed between these cell grips and force was gradually applied till the film broke[16,17] .

The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follows:

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross section area}}$$

Drug content uniformity of patches

The patches ($1 cm^2$) were cut and added to a beaker containing 100 mL of phosphate buffered saline[10] of pH 7.4. The medium was stirred with magnetic bead. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo patches (contains no drug) at 274 nm spectrophotometrically. The experiment was repeated to validate the result.

In vitro drug release studies

In vitro skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 mL[18,19]. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of $1 cm^2$ and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37 ± 0.5^0C. The samples of 1 mL were withdrawn at time interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 14 hrs, analyzed for drug content spectrophotometrically at 274 nm 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

The transdermal patches were transparent, smooth, uniform and flexible. The thickness of the optimized patches was varied from 0.211 ± 0.016 mm to 0.232 ± 0.013 mm. Low standard deviation values in the film thickness measurements ensured uniformity of the patches prepared by evaporation method (Table 2).

The weights ranged between 0.312 ± 0.033 mg and 0.398 ± 0.021 mg, which indicates that different batches patches weights were relatively similar (Table 2).

The % moisture loss was found to be between 5.25 ±1.45 to 12.34 ±1.62 and % moisture absorption was found to be 3.242 ±1.524 to 6.426 ±1.245 (Table 2). The result revealed that the moisture absorption and loss was found to increase with increasing concentration of three polymers. The small moisture loss in the formulations helps the film to remain stable, brittle and free from complete drying. Again low moisture absorption protects the material from microbial contamination and bulkiness of the patches (Table 2).

Folding endurance was found to be >150 that is satisfactory weight of the patches, the folding endurance was found (Table 2) to be between 74.11 ± 4.231 to 97.56 ± 6.231.

The patches prepared from HPMC and carbomer (H4 and H5) show more tensile strength than the patches (Table 3) prepared from SCMC and carbomer (H8 and H10). As the concentration of hydrophilic polymer HPMC, SCMC and carbomer were increased there is increase in tensile strength. The tensile strength measures the ability of patches to with

Table 1.
Composition of Terbinafine HCL trasdermal patch

S. NO	Ingredient (g)	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14
1	Terbinafine HCL	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
2	HPMC	0.1	0.2	0.3	0.4	0.5	0	0	0	0.1	0.2	0.3	0.2	0.3	0.4
3	SCMC	0	0	0	0	0	0.1	0.2	0.3	0.1	0.2	0.3	0.3	0.4	0.5
4	Carbomer 934	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0	0	0	0.3	0.3	0.3
7	Glycerol (%)	10	10	10	10	10	10	10	10	10	10	10	10	10	10
8	Distilled water (ml)	50	50	50	50	50	50	50	50	50	50	50	50	50	50

SCMC-sodium carboxy methyl cellulose
HPMC- hydroxypropyl methyl cellulose

Table 2.
Characteristics of optimized Terbinafine HCL patches

S.No	*Thickness (mm)*	*Weight (g)*	*Folding endurance*	*% moisture absorption*	*% moisture loss*	*Water vapour Transmission rate*
H4	0.210 ± 0.011	0.380 ± 0.023	96.21 ± 4.231	3.254 ± 1.534	9.31 ± 2.21	0.0024 ± 0.0002
H5	0.212 ± 0.013	0.372 ± 0.012	97.56 ± 6.231	3.242 ± 1.524	9.83 ± 1.11	0.0043 ± 0.0005
H8	0.211 ± 0.016	0.391 ± 0.022	74.11 ± 4.231	6.212 ± 1.605	5.72 ± 1.23	0.0031 ± 0.0004
H10	0.210 ± 0.012	0.398 ± 0.021	74.34 ± 8.231	6.426 ± 1.245	5.25 ± 1.45	0.0041 ± 0.0002
H13	0.230 ± 0.014	0.312 ± 0.033	82.14 ± 6.231	4.414 ± 1.508	12.21 ± 1.34	0.0022 ± 0.0001
H14	0.232 ± 0.013	0.324 ± 0.031	82.23 ± 5.231	4.133 ± 1.255	12.34 ± 1.62	0.0047 ± 0.0004

stand rupture. The mean value was found to vary between 3.21 ± 0.114 to 4.62 ± 0.111 kg/mm^2.
The drug content of each formulation (Table 1) was evaluated and the results are shown in Table 3. Drug content in all formulations were found to be uniform ranging from 92.01 to 93.22%. This indicates that the drug was dispersed uniformly throughout the patches.

Table 3.
Results of tensile strength, drug content and *in vitro* drug release

S.No	*Tensile strength (Kg/mm^2)*	*% Drug content*	*% Drug release*
H4	3.91 ± 0.032	92.01	96.21 ± 4.231
H5	3.87 ± 0.013	90.21	97.56 ± 6.231
H8	3.21 ± 0.114	92.11	74.11 ± 4.231
H10	3.31 ± 0.012	92.42	74.34 ± 8.220
H13	4.62 ± 0.111	93.01	82.14 ± 6.241
H14	4.53 ± 0.043	93.22	82.23 ± 5.247

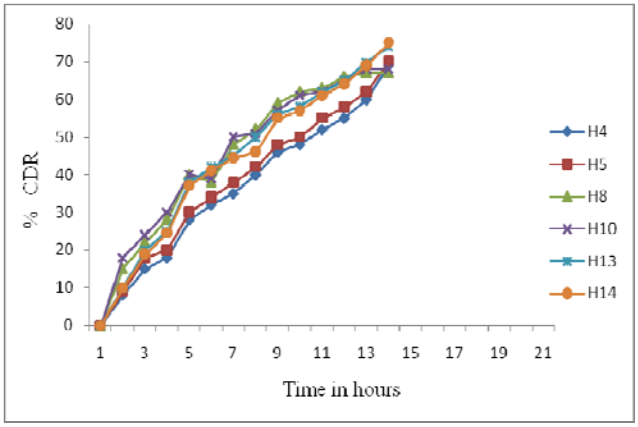

Figure 1. Showing the Diffusion of optimized formulation

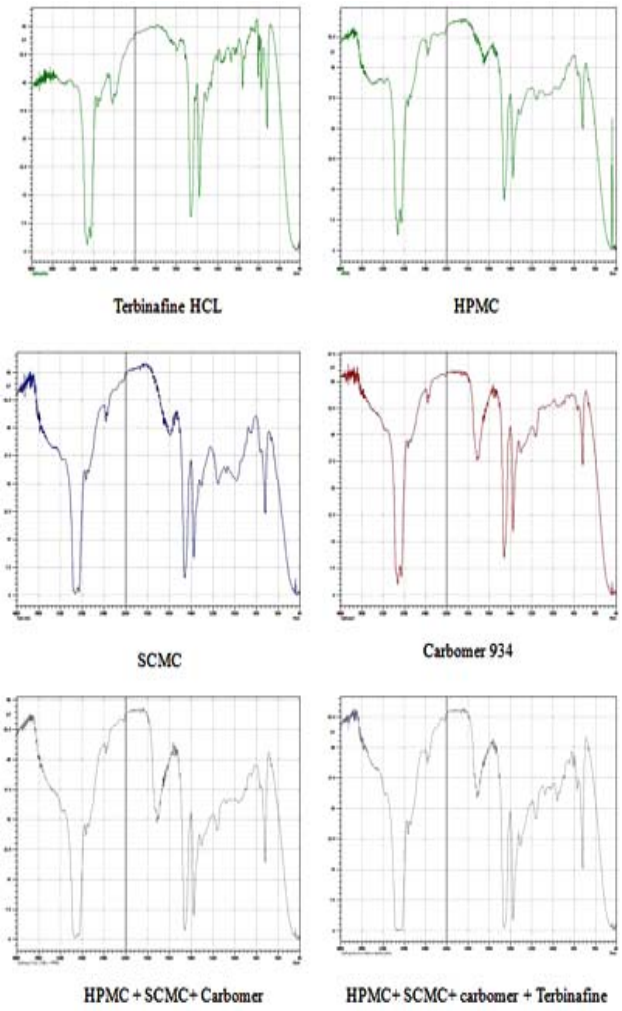

Figure 2: FTIR Spectra of physical mixture

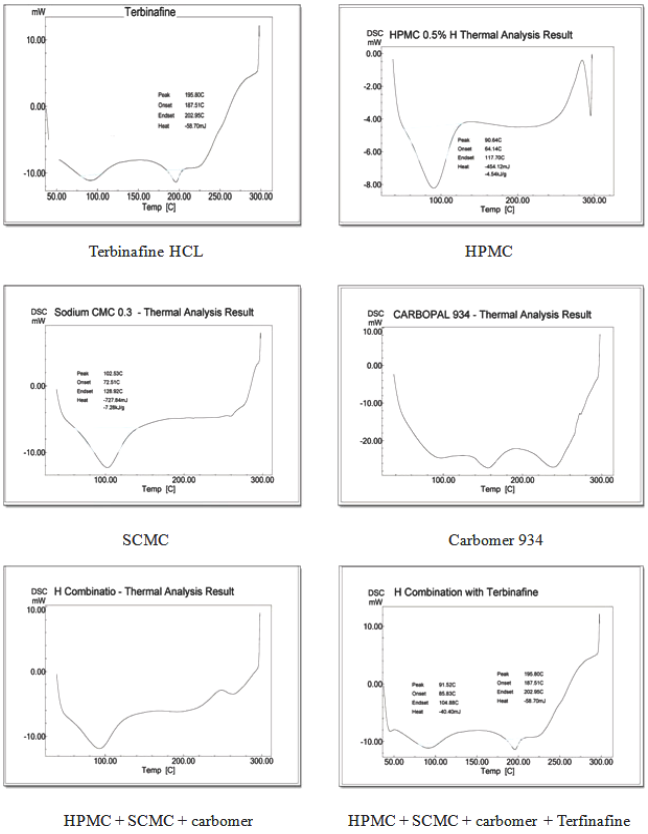

Figure 3. DSC Spectra of physical mixture

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer diffusion on drug release from matrices has been known for ensuring the sustained release performance. The result indicated that the release of drug from patches increases with increasing concentration of HPMC with carbomer. The cumulative percent of drug release in 14 h was found to be the highest (75.521 ± 0.481) from formulation H14 carrying HPMC, SCMC and carbomer (Fig 1) and minimum (67.078 ± 1.025) from formulation H8 carrying SCMC and carbomer.

The initial IR spectra of the drug and the polymers are satisfactory with their characteristic absorption bands; similarly, the physical mixtures also indicate the presence of characteristic peaks of the drug and the polymers. It is clear that he drug and the excipients are free from any significant chemical interactions.

Terbinafine HCL showed an endothermic peak at 195.80, Combination of polymers HPMC, SCMC and carbomer 934 exhibited a peak at 91.52, while that of HPMC, SCMC and carbomer 934 combination of polymers and Terbinafine HCL showed a peak at 91.52 and 195.80. From DSC study it has been found that there is no significant change in drug's melting peak. From the DSC results it has been concluded that drugs and other excipients are compatible which each other and selected for further formulation studies

CONCLUSION

From the results obtained and discussion generated there from, encouraged conclusions were drawn. On the basis of the in vitro characterization it was concluded that Terbinafine could be administered transdermally through matrix type TDDS developed in our laboratory. Transdermal patches consisting of the bioadhesive polymers HPMC,SCMC and cabomer 934 with Terbinafine HCL were effective for nail fungal infection. The drug remained intact and stable in the TDDS during storage, with no significant chemical interaction between the drug and the excipient.

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