INTRODUCTION

In the recent years, considerable attention has been focused on the development of new drug delivery systems. Previously, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. Conventional dosage forms usually provide wide ranging fluctuation in bioavailability of drug leading to the requirement of developing controlled release drug delivery system. Factors such as repetitive dosing and unpredictable absorption lead to the concept of controlled drug delivery system or therapeutic system. Transdermal patches are innovative drug delivery systems intended for skin application to achieve a systemic effect. These are medicated adhesive patches that are placed on the skin to provide clinical benefits like controlled release of the drug, and produce a steady blood-level profile, leading to reduced systemic side effects and improved efficacy over other dosage forms. Transdermal patches offer advantages such as maintenance of constant and prolonged drug level, reduced frequency of dosing, minimization of inter and intra patient variability, self medication, leading to patient compliance. Transdermal systems provide drug systemically at a predictable rate and maintain the rate for extended periods of time thus eliminating numerous problems associated with oral products such as unpredictable or reduced bioavailability, enhanced first pass hepatic metabolism, relatively short residence time, dose dumping and dosing inflexibility. Sertaconazole nitrate is an imidazole/triazole type antifungal agent. Sertaconazole nitrate has a specific mode of action. It interacts with the 14-a 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. The present study was undertaken to formulate the matrix type transdermal patches of sertaconazole nitrate. The polymers used for the preparation of matrix are polyvinyl pyrrolidone (PVPK-30), ethyl cellulose (EC) and dibutyl phthalate as plasticizer.

MATERIALS AND METHODS

Sertaconazole nitrate, Polyvinyl pyrrolidone (PVPK-30) were supplied as a gift sample from Biodeal Pharmaceuticals Pvt. Ltd., (Himachal Pradesh, India), Ethyl cellulose, n-dibutyl phthalate and chloroform were purchased from S.D. Fine Chemicals, Mumbai, India. Tris buffer was purchased from RFCL, New Delhi, India and Sodium Lauryl Sulfate (SLS) was purchased from Qualigens Fine Chemicals, Navi Mumbai, India. All chemicals, solvents and reagents were used of either pharmacopeial or analytical grade.

Characterization & Compatibility Study of drug and excipients

FTIR spectra of pure sertaconazole nitrate and physical mixture of drug and excipients were recorded on FTIR-8400S, Shimadzu, (Tokyo, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. The mixture of sertaconazole nitrate, polyvinyl pyrrolidone and ethyl cellulose was taken and pellet was prepared for spectroscopic studies. Each spectrum was derived from single average scans collected in the region of 400-4000 cm⁻¹ at spectral resolution of 4 cm⁻² and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu. Preparation of transdermal patches

Matrix type transdermal patches composed of different ratios of Ethyl cellulose and PVPK-30 were prepared by solvent evaporation technique in a petri dish. The bottom of the ring was wrapped with aluminum foil on which backing membrane was cast by pouring 4% w/v polyvinyl alcohol solution followed by drying at 60°C for 6h. Dibutyl phthalate was incorporated as a plasticizer at 30% w/w of dry weight of polymer. Backing membrane was casted by pouring and allowing to evaporate 4% aqueous solution
of polyvinyl alcohol in petri dish at 60°C for 6h. The matrix was prepared by pouring the homogenous dispersion of drug with different blends of ethyl cellulose with PVPK-30 in chloroform on the backing membrane in petri dish. The above dispersion was evaporated slowly and uniformly at 40°C for 2h with inverted funnel on the dispersion to achieve a drug polymer matrix patch. The patches were again dried at 60°C for 30 min for complete drying. The dry patches were kept in dessicators until use1-3 [Table 1].

Table 1: Composition of Formulation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Polymeric Blend</th>
<th>Ratio of Polymer (W/W)</th>
<th>Total weight of polymer in mg</th>
<th>Drug %w/w of polymer</th>
<th>Plasticizer dibutyl phthalate</th>
<th>Solvent system</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>PVP:EC</td>
<td>1:1</td>
<td>660</td>
<td>10</td>
<td>30%</td>
<td>Chloroform</td>
</tr>
<tr>
<td>F2</td>
<td>PVP:EC</td>
<td>1:2</td>
<td>600</td>
<td>10</td>
<td>30%</td>
<td>Chloroform</td>
</tr>
<tr>
<td>F3</td>
<td>PVP:EC</td>
<td>1:3</td>
<td>600</td>
<td>10</td>
<td>30%</td>
<td>Chloroform</td>
</tr>
<tr>
<td>F4</td>
<td>PVP:EC</td>
<td>1:5</td>
<td>600</td>
<td>10</td>
<td>30%</td>
<td>Chloroform</td>
</tr>
<tr>
<td>F5</td>
<td>PVP:EC</td>
<td>2:3</td>
<td>600</td>
<td>10</td>
<td>30%</td>
<td>Chloroform</td>
</tr>
</tbody>
</table>

Solubility measurement
Solubility of sertaconazole nitrate was determined at several values of pH, viz., 4.0, 5.0, 6.0, 7.4, 8.0, and 9.0. Excess of sertaconazole nitrate was added to 10 mL of buffer solutions.

At each level, the samples were stirred in a conical flask for 24h at 37°C. The suspension were filtered using a 0.45 micron Whatman filter paper. The concentration of sertaconazole nitrate in the filtrate was determined spectrophotometrically by measuring at 303 nm 1.

Partition coefficient of drug in octanol/water system
The partition coefficient of the drug was determined by taking equal volume of 1-octanol and aqueous solution in a separating funnel. In case of water soluble drugs, a drug solution of 25µg/ml was prepared in distilled water and in case of water insoluble drugs, a drug solution of 25µg/ml was prepared in 1-octanol. Twenty-five milliliters of this solution was taken in a separating funnel and shaken with equal volume of 1-octanol/water system for 30 min and allowed to stand for an hour. The mixture was then centrifuged at 2000 rpm for 10 min and concentration of drug in each phase was determined spectrophotometrically by measuring absorbance at 303 nm. The partition coefficient (Kp) was calculated from the following equation1.

Partition coefficient (Kp) = Conc. of drug in organic phase/Conc. of drug in aqueous Phase

Physicochemical properties of the films

Thickness
The thickness of the patch was determined using digital vernier calliper (Mitutoyo, Tokyo, Japan), recording mean of 5 determinations2-6.

Weight variation
Each film was weighed individually and average weight of three films was found out.

Percent moisture absorption
The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. In the present study the moisture absorption capacity of the films were determined in the following manner. The films were placed in the humidity chamber, keeping the humidity inside the chamber at 75% R.H. After 3 days the films were taken and weighed. The percentage moisture absorption of three films was found by applying following formula2-6.

% Moisture absorption= Final weight – Initial weight/Initial weight x 100

Percent moisture content
The prepared films were marked, then weighed individually and kept in a dessicator containing activated silica at room temperature for 24h. The films were weighed again and again individually until it showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight2-6.

Folding endurance
Folding endurance of patches was determined by repeatedly folding a small strip of film (2cm x 2cm) at the same place till it is broken. The number of time the film could be folded at the same place without breaking was the folding endurance value2-6.

Flatness
Longitudinal strips were cut out from each film, one from the center and two from either side. The length of each strip was measured and the variation in flatness was measured by determining percent constriction, considering 0% constriction is equivalent to 100% flatness.

% Constriction = l1/l2 x 100

l1 = initial length of each strip.

l2 = final length of each strip.

In vitro diffusion study
Franz’s diffusion cell was used for the study of in vitro release patterns of the prepared patches. The diffusion medium is prepared of buffer of pH 7.4. A cellophane membrane is used as a barrier between the donor and receptor compartment. The films were placed between the donor and receptor compartment in such a way that the drug releasing surface faced the receptor compartment. The receptor compartment were filled with the buffer having pH 7.4 and a small bar magnet was used to stir the medium with the help of a magnetic stirrer. The temperature of the diffusion medium was maintained and controlled at 37°C ± 1°C by a thermostatic arrangement. A sample of 5ml was withdrawn at predetermined intervals, being replenished by equal volumes of diffusion medium. Withdrawal of samples was carried out for a period of 24h. The drug concentration in the sampled diffusion medium was determined spectrophotometrically and was calculated with the help of a standard calibration curve and the data was shown in Figures5.

Data analysis
The pharmaceutical dosage forms that do not disaggregate and release the drug slowly could be represented by a zero-order kinetic equation. Analysis of drug release from transdermal system must be performed with a flexible model that can identify the contribution to overall kinetics. Dissolution data was treated with different release kinetic equations.

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% Release of Sertaconazole nitrate

0 10 20 30 40 50 60 70 80 90

0 10 20 30 40 50 60 70 80 90

% Drug Release

Time in Hour

Time in hour

Figure -1 Drug release from formulation F1

Figure -2 Drug release from formulation F2

Figure -3 Drug release from formulation F3

Figure -4 Drug release from formulation F4

Figure -5 Drug release from formulation F5

Figure 1 to 5 showing the % of sertaconazole release from the formulated patches

Chart showing % moisture content of patch

% Moisture content

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

F1 F2 F3 F4 F5

Chart showing thickness of different formulation

Thickness

0.17 0.18 0.19 0.2

F1 F2 F3 F4 F5

Figure -6 Showing thicknesses of patches

Figure -7 Showing Endurances of patches
RESULTS AND DISCUSSION

In the present study efforts were made to prepare transdermal patches of sertaconazole nitrate by using different ratios of polymers such as Polyvinyl pyrrolidone (PVP K-30) and ethyl cellulose. Here dibutylphthalate is used as a plasticizer. The prepared formulations were subjected to various physicochemical characteristics such as thickness, weight variation, percent moisture absorption, percent moisture content, flatness and folding endurance. The release pattern of formulations were studied in Franz’s diffusion apparatus using cellophane membrane.

Moisture content and moisture uptake can cause significant changes in properties such as reduced crushing strength, increased pore diameter in the patches containing polymer. But the moisture content in our preparations was found to be low, and it varied very little in the formulations. The little moisture content helps the formulations to be stable and prevents them from becoming a completely dried, brittle product. Low moisture uptake also protects the materials from microbial contamination and avoids bulkiness of the patches.

In order to evaluate the flexibility the film were subjected to folding endurance. The values in the range that prepared films were observed batches having capability to withstand the mechanical pressure along with good flexibility.

The diffusion studies of patches containing different ratios of polymers were done using Franz’s diffusion cell. The revealed data shows that the drug release pattern of formulation 4 shows drug release in a

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Table 2: Evaluation of transdermal patches of Sertaconazole nitrate

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness</th>
<th>Folding Endurance</th>
<th>%Moisture Content</th>
<th>%Moisture Uptake</th>
<th>Flatness</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.18 ± 0.03</td>
<td>104 ± 3</td>
<td>2.73 ± 0.14</td>
<td>4.98 ± 0.25</td>
<td>100%</td>
</tr>
<tr>
<td>F2</td>
<td>0.18 ± 0.02</td>
<td>118 ± 4</td>
<td>2.86 ± 0.42</td>
<td>4.77 ± 0.36</td>
<td>100%</td>
</tr>
<tr>
<td>F3</td>
<td>0.19 ± 0.04</td>
<td>129 ± 2</td>
<td>2.34 ± 0.21</td>
<td>5.58 ± 1.03</td>
<td>100%</td>
</tr>
<tr>
<td>F4</td>
<td>0.19 ± 0.03</td>
<td>152 ± 2</td>
<td>2.68 ± 0.34</td>
<td>5.22 ± 0.53</td>
<td>100%</td>
</tr>
<tr>
<td>F5</td>
<td>0.20 ± 0.02</td>
<td>98 ± 3</td>
<td>3.16 ± 0.32</td>
<td>4.03 ± 0.98</td>
<td>100%</td>
</tr>
</tbody>
</table>

Zero-order release equation

\[ Q = k_o t \]

Higuchi’s square root of time equation

\[ Q = k_H \sqrt{t} \]

First-order release equation

\[ \log Q_t = \log Q_0 + Kt/2.303 \]

Korsmeyer-Peppas equation

\[ F = (M_t/M) = K_0 t^n \]

Where Q is the amount of drug release at time t; M, is drug release at time t; M is the total amount of drug in dosage form; F is fraction of drug release at time t; K_0 is zero-order release rate constant; K_H is Higuchi square root of time release rate constant; K_0 is a constant dependent on geometry of dosage form; and n is diffusion exponent indicating the mechanism of drug release. If the value of n is 0.5, it indicates fickian diffusion; if between 0.5 and 1.0, anomalous transport; 1.0 indicates case-II transport; and higher than 1.0, super case-II transport.

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controlled manner, as it fits into the Kosmeyers-peppas rule. The formulation 4 shows cumulative release of drug of 71.21%.

**CONCLUSION**
Formulation 4 was found to be the best among all batches because of its consistent release rate and extent of drug release. The formulation 4 has achieved the object to extended release reduced frequency of administration, avoids the first pass effect and thus may improve the patient compliance.

**ACKNOWLEDGEMENT**
We are thankful to Biodeal Pharmaceuticals Pvt. Ltd. for their support and kind cooperation for my work.

**REFERENCES**

Source of support: Nil, Conflict of interest: None Declared