INTRODUCTION
The fundamentals of a successful pharmaceutical formulation are to enable delivery of the active substance to the target organ at therapeutically relevant levels, with negligible discomfort and side effects to the patient.\cite{1,2} The drug delivery system should deliver the drug at a rate dictated by the needs of the body over a specified period of treatment.\cite{3} Transdermal Drug Delivery System (TDDS) is self-contained, discrete dosage form that, when applied to intact skin is designed to deliver the drug(s) through the skin to the systemic circulation. The limitations of oral route can be overcome by transdermal route and benefits of intravenous drug infusion such as to bypass hepatic “first-pass” elimination to maintain constant prolong and therapeutic effective drug level in the body can be closely duplicated without its hazards by using the intact skin as a port of drug administration.\cite{4} Promethazine hydrochloride though possessing 88% of bioavailability however undergoes tremendous hepatic “first-pass” metabolism and thus the absolute bioavailability is only 25%. Thus the problem associated with promethazine hydrochloride will be overcome by formulating it into transdermal film.

The objective of the present study was to evaluate effect of formulation variables on in vitro characters of Promethazine hydrochloride transdermal film.

MATERIAL AND METHODS
Materials
Promethazine hydrochloride was obtained as gift sample from Sehat Pharma Pvt. Ltd., Gujarat. Eudragit RS 100 and Eudragit RL 100 were obtained as a gift samples from Evonik Pharma, Mumbai. Potassium dihydrogen phosphate, Ethanol, Methanol and Acetone were purchased from Loba Chemie, Mumbai. Sodium chloride and Potassium chloride purchased from S. D. Fine Chemicals, Mumbai. All the other chemicals, reagents and solvents used were of AR grade.

Methods
Formulation of transdermal film
The transdermal films of Promethazine hydrochloride were prepared by solvent evaporation method. The
weighed quantities of polymers were taken in a beaker and then the measured quantity of acetone was added. The measured quantity of ethanol was taken into another beaker and weighed quantity of Promethazine hydrochloride, Dibutyl pthalate and Dimethyl sulfoxide were added. Ascorbic acid was dissolved separately in methanol and was then added in the beaker containing Promethazine hydrochloride. The solutions in a two beakers were mixed and filled in the transdermal ring. The ring was covered with funnel so as to prevent it from rapid drying and dried at room temperature in a dust-free environment for 24 h. The film was removed from the ring when properly dried carried out for evaluation tests. The transdermal patches were stored in a desiccators containing fused calcium chloride until further use.[5]

**Table 1:** Composition of Promethazine hydrochloride polymeric transdermal films

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Promethazine Hydrochloride (mg)</th>
<th>Eudragit 100 (RS:RL) (mg)</th>
<th>Dibutyl pthalate (mg)</th>
<th>Dimethyl sulfoxide (mg)</th>
<th>Acetone: Ethanol: Methanol (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>53</td>
<td>100:200</td>
<td>30</td>
<td>15</td>
<td>2:2:1</td>
</tr>
<tr>
<td>F2</td>
<td>53</td>
<td>150:150</td>
<td>30</td>
<td>15</td>
<td>2:2:1</td>
</tr>
<tr>
<td>F3</td>
<td>53</td>
<td>200:100</td>
<td>30</td>
<td>15</td>
<td>2:2:1</td>
</tr>
<tr>
<td>F4</td>
<td>53</td>
<td>250:50</td>
<td>30</td>
<td>15</td>
<td>2:2:1</td>
</tr>
<tr>
<td>F5</td>
<td>53</td>
<td>50:250</td>
<td>30</td>
<td>15</td>
<td>2:2:1</td>
</tr>
<tr>
<td>S1</td>
<td>53</td>
<td>50:150</td>
<td>20</td>
<td>10</td>
<td>2:2:1</td>
</tr>
<tr>
<td>S2</td>
<td>53</td>
<td>100:100</td>
<td>20</td>
<td>10</td>
<td>2:2:1</td>
</tr>
</tbody>
</table>

**Evaluation of transdermal films**

**Weight variation**

The transdermal films were subjected to weight variation by individually weighing 5 transdermal films of same formulation. Such determinations were carried out for each formulation of Promethazine hydrochloride transdermal film.[5]

**Thickness**

The thicknesses of transdermal films were measured by using screw gauge. The thickness was measured at five different points on the same film and average of five readings was taken.[5]

**Folding endurance**

It was determined by repeatedly folding the transdermal film at the same place until it broke. The test was carried out to check the efficiency of the plasticizer and the strength of the film, prepared using varying ratios of the polymers. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.[5]

**Flatness and appearance**

Longitudinal strips were cut out from each transdermal film, one from the center and two from either side. The length of each strip was measured. The variation in the length because of non-uniformity in flatness was measured by determining % constriction, considering 0% constriction is equivalent to 100% flatness.[5]

\[
\% \text{ Constriction} = \frac{L_1 - L_2}{L_2} \times 100
\]

Where \( L_1 = \) initial length of each strip
\( L_2 = \) final length of each strip

**Percentage moisture absorption**

A weighed transdermal film was kept in a desiccator and exposed to 84% RH (a saturated solution of aluminum chloride) at room temperature for 24 h. It was taken out and weighed until a constant weight for the film was obtained. The % of moisture absorption was calculated as the difference between final and initial weight with respect to initial weight.[5]

\[
\% \text{ Moisture absorption} = \frac{\text{final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]
Percentage moisture content

The transdermal films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 h. Individual transdermal films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to initial weight.\[5\]

\[
\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

Percentage moisture loss

Accurately weighed transdermal films of each formulation batch were kept in a desiccator and exposed to an atmosphere of 98% RH (containing anhydrous calcium chloride) at room temperature and weighed after 3 d. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight.\[5\]

\[
\% \text{ Moisture loss} = \frac{\text{weight Initial} - \text{weight Final}}{\text{weight Initial}} \times 100
\]

Water vapor transmission rate (WVT Rate)

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. Then, in these dried cells about 1 g anhydrous calcium chloride was placed and the polymer film from each batch of formulation was fixed over the brim. The cells were accurately weighed and kept in a closed desiccators containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 24 h of storage.\[5\]

\[
\text{Water vapor transmission rate} = \frac{\text{Weight Initial} - \text{Weight Final}}{\text{Time} \times \text{Area}}
\]

Drug content

A transdermal patch was cut into 5 equal parts and put in a 50 ml buffer (pH 7.4). This was then shaken in a mechanical shaker for 24 h to get a homogeneous solution and filtered. The drug content was determined spectrophotometrically at 249.5 nm after suitable dilution.\[5\]

Table 2: Physico-chemical evaluation of transdermal films of Promethazine hydrochloride

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Percent moisture absorption (%)±S.D</th>
<th>Percent moisture loss (%)±S.D</th>
<th>Percent moisture content (%)±S.D</th>
<th>Thickness (mm)±S.D</th>
<th>Weight uniformity (mg)±S.D</th>
<th>Folding endurance ± S.D.</th>
<th>Water vapor transmission ±S.D</th>
<th>Drug content ±S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.59±0.144</td>
<td>1.43±0.27</td>
<td>1.2±0.185</td>
<td>463±2.3</td>
<td>28.4±1.35</td>
<td>1.36±0.057×10^-4</td>
<td>99.12±0.32</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>1.06 ±0.17</td>
<td>1.52±0.25</td>
<td>1.39±0.18</td>
<td>465.6±2.9</td>
<td>43±1.098</td>
<td>1.84±0.014×10^-4</td>
<td>98.65±0.19</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>0.89±0.133</td>
<td>1.68±0.28</td>
<td>1.85±0.06</td>
<td>469.8±2.4</td>
<td>47.8±0.971</td>
<td>2.56±0.28×10^-4</td>
<td>98.70±0.40</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>0.59±0.118</td>
<td>1.65±0.23</td>
<td>1.59±0.01</td>
<td>464.5±2.2</td>
<td>50.4±1.02</td>
<td>2.70±0.28×10^-4</td>
<td>98.77±0.50</td>
<td></td>
</tr>
<tr>
<td>F5</td>
<td>0.95±0.082</td>
<td>1.58±0.3</td>
<td>1.9±0.057</td>
<td>469.2±1.9</td>
<td>28.5±0.74</td>
<td>1.58±0.052×10^-4</td>
<td>99.07±0.16</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>1.1 ± 0.237</td>
<td>1.56±0.34</td>
<td>2.05±0.11</td>
<td>371.5±1.1</td>
<td>41.2±1.16</td>
<td>2.41±0.04×10^-4</td>
<td>98.3±0.179</td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>1.35±0.292</td>
<td>1.39±0.23</td>
<td>2.27±0.37</td>
<td>364.6±1.3</td>
<td>46.4±0.81</td>
<td>3.68±0.074×10^-4</td>
<td>98.78±0.56</td>
<td></td>
</tr>
</tbody>
</table>

In vitro drug release (dissolution study)

A modified stainless steel disc assembly (USP Apparatus 5, paddle over disc assembly), was used for the assessment of the release of the drug from the transdermal films. The transdermal drug delivery system (TDDS) was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was pH 7.4 buffer solution and the apparatus was equilibrated to 37±0.5°C. The apparatus was operated at 50 rpm. Samples were withdrawn at appropriate time intervals up to 12 h and were filtered through Whatman filter paper no. 42 and then filter through membrane filter (0.2μ) and analyzed for absorbance by using UV-Visible spectrophotometer (UV–1601) at 249.5 nm after suitable dilution. Cumulative % drug release were calculated and plotted against time.\[6\]
Table 3: Cumulative % drug release from various formulation batches

<table>
<thead>
<tr>
<th>Formula/Time (h)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>S1</th>
<th>S2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>11.62±0.012</td>
<td>9.21±0.012</td>
<td>10.32±0.044</td>
<td>6.21±0.073</td>
<td>20.34±0.294</td>
<td>10.12±0.034</td>
<td>12.21±0.087</td>
</tr>
<tr>
<td>2</td>
<td>14.32±0.024</td>
<td>15.32±0.035</td>
<td>15.52±0.045</td>
<td>10.31±0.026</td>
<td>35.21±0.025</td>
<td>13.27±0.098</td>
<td>14.39±0.026</td>
</tr>
<tr>
<td>3</td>
<td>20.11±0.024</td>
<td>20.21±0.033</td>
<td>16.91±0.034</td>
<td>15.51±0.039</td>
<td>55.21±0.026</td>
<td>19.18±0.026</td>
<td>17.82±0.042</td>
</tr>
<tr>
<td>4</td>
<td>32.62±0.023</td>
<td>35.31±0.037</td>
<td>20.62±0.074</td>
<td>18.62±0.011</td>
<td>45.37±0.062</td>
<td>35.21±0.025</td>
<td>21.32±0.025</td>
</tr>
<tr>
<td>5</td>
<td>40.18±0.026</td>
<td>38.92±0.016</td>
<td>24.81±0.047</td>
<td>22.31±0.037</td>
<td>13.27±0.098</td>
<td>25.32±0.026</td>
<td>25.69±0.013</td>
</tr>
<tr>
<td>6</td>
<td>46.29±0.013</td>
<td>44.62±0.018</td>
<td>34.32±0.016</td>
<td>25.11±0.017</td>
<td>45.32±0.026</td>
<td>45.32±0.014</td>
<td>35.72±0.021</td>
</tr>
<tr>
<td>7</td>
<td>55.39±0.012</td>
<td>53.21±0.012</td>
<td>39.11±0.044</td>
<td>28.62±0.073</td>
<td>75.21±0.024</td>
<td>55.12±0.034</td>
<td>49.37±0.087</td>
</tr>
<tr>
<td>8</td>
<td>59.92±0.024</td>
<td>62.12±0.035</td>
<td>44.62±0.045</td>
<td>33.39±0.026</td>
<td>79.19±0.025</td>
<td>65.32±0.098</td>
<td>51.62±0.026</td>
</tr>
<tr>
<td>9</td>
<td>63.43±0.024</td>
<td>65.32±0.033</td>
<td>49.81±0.034</td>
<td>38.62±0.039</td>
<td>83.12±0.062</td>
<td>67.45±0.026</td>
<td>53.88±0.042</td>
</tr>
<tr>
<td>10</td>
<td>65.32±0.023</td>
<td>66.11±0.037</td>
<td>52.45±0.074</td>
<td>42.18±0.011</td>
<td>88.96±0.026</td>
<td>68.74±0.015</td>
<td>53.88±0.025</td>
</tr>
<tr>
<td>11</td>
<td>72.91±0.026</td>
<td>66.98±0.016</td>
<td>54.12±0.034</td>
<td>45.32±0.037</td>
<td>93.33±0.047</td>
<td>69.45±0.014</td>
<td>57.98±0.013</td>
</tr>
<tr>
<td>12</td>
<td>78.06±0.013</td>
<td>67.67±0.018</td>
<td>59.58±0.016</td>
<td>47.75±0.017</td>
<td>96.45±0.016</td>
<td>71.85±0.027</td>
<td>61.68±0.021</td>
</tr>
</tbody>
</table>

Each value represents mean±SD, n = 5

Table 4: Drug release kinetics for the various formulation batches

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi’s model</th>
<th>Peppa’s model</th>
<th>Diffusion coefficient (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.962</td>
<td>0.948</td>
<td>0.906</td>
<td>0.990</td>
<td>0.495</td>
</tr>
<tr>
<td>F2</td>
<td>0.981</td>
<td>0.929</td>
<td>0.903</td>
<td>0.992</td>
<td>0.467</td>
</tr>
<tr>
<td>F3</td>
<td>0.965</td>
<td>0.878</td>
<td>0.921</td>
<td>0.989</td>
<td>0.498</td>
</tr>
<tr>
<td>F4</td>
<td>0.972</td>
<td>0.981</td>
<td>0.940</td>
<td>0.986</td>
<td>0.449</td>
</tr>
<tr>
<td>F5</td>
<td>0.979</td>
<td>0.910</td>
<td>0.915</td>
<td>1.004</td>
<td>0.502</td>
</tr>
<tr>
<td>S1</td>
<td>0.968</td>
<td>0.887</td>
<td>0.876</td>
<td>0.981</td>
<td>0.455</td>
</tr>
<tr>
<td>S2</td>
<td>0.986</td>
<td>0.959</td>
<td>0.883</td>
<td>0.988</td>
<td>0.459</td>
</tr>
</tbody>
</table>

Optimized formula for Promethazine hydrochloride transdermal film

Batch F5, composing of polymer ERS 50: ERL 250 was found to be stable and to release the drug (96.45%) up to 12 h and possess good physicochemical properties, hence was considered optimized batch for further in vitro diffusion study and scanning electron microscopy.

**In vitro diffusion study**

In vitro diffusion study was performed in a Franz diffusion assembly of capacity 10 ml using cellophane membrane (Dialysis membrane 70). A section of membrane was cut, measured and placed on the dermal side of the membrane in the donor compartment facing the drug matrix side of the transdermal film to the membrane and backing membrane upward. The holder containing the membrane and formulation was placed on the receiver compartment of the cell, containing phosphate buffer pH 7.4. The temperature of the diffusion cell was maintained at 37±0.5°C by circulating water jacket. The solution in the receiver compartment was constantly and continuously stirred during the whole experiment using magnetic bead. The samples were withdrawn (1 ml) at different time intervals and an equal amount of phosphate buffer pH 7.4 was replaced. Absorbance of the samples was recorded spectrophotometrically at 249.5 nm using phosphate buffer solution, pH 7.4, as a blank.[7]

The cumulative percentage of drug diffused at each time interval was calculated. The plot of % cumulative drug diffused Vs. time (h), cumulative amount of drug permeated...
(μg/cm²)/h V/s time (h) and flux V/s time (h) were plotted.

**Figure 1**: *In vitro* diffusion of Promethazine hydrochloride from formulation batch F5

**Figure 2**: *In vitro* diffusion of Promethazine hydrochloride from formulation batch F5

**Figure 3**: *In vitro* diffusion flux of Promethazine hydrochloride from formulation batch F5

Scanning electron microscopy (SEM)
The external morphology of the transdermal film was investigated by Scanning Electron Microscopy (SEM) using JSM 6380A (JOEL, Japan). Transdermal film of suitable size was cut and fixed over brass brim. It was then coated with platinum by ion sputtering using auto fine coater JFC-1600 for 20s at 1.1v under argon atmosphere and then mounted onto metal stubs using double-sided carbon adhesive tape and the scanning electron micrograph was taken.

RESULTS AND DISCUSSION

**Formulation of transdermal film**
The matrix-type controlled transdermal drug films were prepared by solvent evaporation method using Acetone: ethanol (1:1) as solvent for ERL 100 and ERS 100. The casting solution was prepared by using 6% w/v polymer in solvent system. Ascorbic acid was used as an anti-oxidant and was dissolved in methanol. DBP was used as a plasticizer and DMSO as penetration enhancer. The formulation of different batches of Promethazine hydrochloride polymeric transdermal films are shown in Table 1. The prepared transdermal films were evaluated for its physicochemical properties, *in vitro* dissolution studies, short term stability studies, *in vitro* permeation study and scanning electron microscopy.

**Moisture absorption and moisture content**
The results of moisture absorption and moisture content studies are shown in Table 2. The moisture absorption in the formulation batches ranges from 0.59 ± 0.114 to 0.95 ± 0.082 % and 1.10 ± 0.237 to 1.35 ± 0.292 % (for formulation F series and formulation S series respectively). The moisture content in the transdermal film ranges from 1.43 ± 0.27 to 1.68 ± 0.28 % and 1.392 ± 0.23 to 1.56 ± 0.36% (for formulation F series and formulation S series respectively). The results revealed that the moisture absorption and moisture content was found to be increased with increased concentration of hydrophilic polymer (Eudragit RL).
Percentage moisture loss

The results of percentage moisture loss study are shown in Table 2. The percent moisture loss in the formulations batches ranges from 1.2 ± 0.185 to 1.9 ± 0.057 and 2.05 ± 0.109 to 2.27 ± 0.372. The results revealed that the moisture loss was found to be increased with increased concentration of hydrophilic polymer (Eudragit RL). The smaller moisture content in the formulations helps them to remain stable and from being a completely dried and brittle patch.

Water vapor transmission rate

The results of water vapor transmission rate are shown in Table 2. Water vapor transmission rate appeared maximum with the film formulated with Eudragit RS 100 in 5:1 Eudragit RL 100. As anticipated, with decreased in Eudragit RL 100 concentration the values of percentage water vapor transmission rate increased in accordance with their increasing hydrophobic nature. The transdermal film F5 having Eudragit RS 100: Eudragit RL 100 in (1:5) ratio was having least % water vapor transmission rate.

Mass variation

The results of mass variation study were found to vary between 463 ± 2.30 to 469.8 ± 2.38 mg and 364.6 ± 1.29 to 371.5 ± 1.11 mg respectively for F series S series respectively. The results indicated that formulation batches F3 and S1 were having highest mass, while formulation batches F1 and S2 was having the least mass among the formulation batches.

Thickness

The results of thickness study carried for the films are shown in (Table 2), which indicates that the thickness of the transdermal films varied from 0.14 ± 0.006 to 0.22 ± 0.008 mm. Formulation F1 was having the maximum thickness i.e. 0.22 ± 0.008 mm while S1 was having the least 0.14 ± 0.006 mm.

Folding endurance

Folding endurance study was carried out (Table 2) and results ranged from 28.4 ± 1.350 to 50.4 ± 1.019 and 41.2 ± 1.160 to 46.4 ± 0.804 for formulation F series and formulation S series respectively. Folding endurance test results indicates that the transdermal films would maintain the integrity with general skin folding when applied.

Appearance and flatness study

Appearance and flatness study indicates, the formulations F1 and F5 were having slightly hazy appearance, while the others were transparent. Flatness study indicated that all the formulations were 100% flat in nature. Flatness test results indicated that the transdermal films would adhere to the skin surface properly.

Drug content

The drug content analysis of the prepared formulations (Table 2) had shown that the process adopted for casting the transdermal films was capable of giving patches with uniform drug content and with minimum intra batch variability.

In vitro dissolution study

In vitro dissolution study as shown in (Table 3) indicates that formulation F5 (96.45%) was having more release as compared to other formulations. In the present study it was observed that, as the concentration of hydrophilic polymer (Eudragit RL 100) decreased in the formulations, the drug release rate was decreased substantially, however it was very nominal in formulation F5. It also suggested that, the addition of hydrophilic component to an insoluble film former tends to enhance the release rate. Hence comparing all the data and release profiles, formulation batch F5 among the series was chosen as good release.

The in vitro release profiles were applied on various kinetic models in order to find out the mechanism of drug release (Table 4). The best fit with the highest correlation coefficient was shown in zero-order followed by first order and than by Higuchi’s equations. The rate constants were calculated from the slope of the respective plots. The data obtained were also put in Korsmeyer-Peppa’s model in order to find out n value, which described the drug release mechanism. The n value of transdermal films of different formulation batches were ranged between

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0.449 and 0.502, indicating that the mechanism of drug release was Fickian transport.

**In vitro diffusion study**

The plot of % cumulative drug diffused Vs. time (h), cumulative amount of drug permeated (µg/cm²)/h V/s time (h) and flux V/s time (h) are revealed in Figure 1 to 3. The in vitro diffusion study indicates that cumulative percentage diffusion of F5 formulation batch is 95.14 ± 0.120 in 12 h.

**Scanning electron microscopy (SEM)**

Scanning electron microscopy (SEM) was performed for F5 formulation batch (Figure 4) revealed the surface morphology of the transdermal film. It had shown the uniform distribution of drug in the entire polymer matrix.

**CONCLUSION**

Promethazine hydrochloride possesses all requisite qualities required for controlled drug delivery system in the form of transdermal films. The polymers selected were non-toxic, non-absorbable and they did not lose their film forming properties, when formulated with the drug and excipients. The ERL polymer swells more than ERS due to its higher concentration of hydrophilic quaternary groups. Transdermal films of various polymeric combinations were having little or no apparent effect on physicochemical characteristics among themselves. Among the various polymeric ratios the formulation F5 comprising of polymers ERL 100 and ERS 100 in 5:1 ratio had shown a maximum release 95.15% in controlled manner up to 12 h. Formulation F5 followed Korsmeyer-Peppa's model in dissolution study. It fulfilled the requirement of good TDDS. The transdermal films were transparent and the drug remained homogeneously dispersed in the polymer matrix and is safe to use via transdermal route.

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