ABSTRACT
Trandolapril is an antihypertensive agent which undergoes extensive first pass metabolism making it a possible candidate for transdermal delivery. Patches were prepared using hydroxypropylmethylcellulose, eudragit RL 100, gantrez and carbopol. The results of FTIR and DSC revealed no interaction between drug and polymers. The loss of moisture and uptake of moisture were within the limits. The formulations showed an extended release of the drug upto period of 24 hours during in vitro permeation studies and showed non-Fickian drug release. Stability of the optimized formulation was investigated as per ICH guidelines and was found to be stable with respect to drug content and in vitro permeation.

Keywords: In vitro permeation, Franz diffusion cell, Moisture uptake, Non-Fickian diffusion, Trandolapril.

INTRODUCTION
Transdermal administration refers to continuous drug infusion through an intact skin surface to control the delivery of drug[1]. Transdermal drug delivery is a non-invasive delivery of medicament from the surface of the skin[2]. This has advantages over the oral route of administration, in patient compliance and bypassing first pass metabolism. Several drugs were explored for the possible use in transdermal drug delivery for treating hypertension. A few of these include nifedipine[3], metaprolol[4] and isradipine[5].

Trandolapril is an angiotensin converting enzyme inhibitor, orally active and undergoes substantial first-pass metabolism by cytochrome P450 enzymes. The terminal half-life of trandolapril is about 0.8 to 1 hour[6]. Following oral administration, trandolapril is well-absorbed and undergoes substantial first-pass metabolism; the systemic bioavailability of trandolapril is about 4–14%[7]. In view of these facts, this drug can be considered as a suitable candidate for buccal delivery.

MATERIALS AND METHODS
Trandolapril was a gift from Hetero Drugs Ltd., (Hyderabad, India). Eudragit was generous gift from Colorcon Asia Pvt Ltd., (Goa, India); Gantrez International Specialty Products (Hyderabad, India). Carbopol was gifted by Inventis Drug Delivery Systems Pvt Ltd., (Hyderabad, India). All reagents were used of analytical grade.

Animals
Male Wistar rats weighing approximately 200–250 g were used for the diffusion studies of trandolapril transdermal patches. The animals were supplied with food and water ad libitum. The animal studies were approved by the Institute Animal Ethics Committee (IAEC), Regd no. 1434/PC/a/11 CPCSEA and all
experiments were conducted as per the norms of the Committee for the Purpose of Supervision of Experiments on Animals, India.

**Investigation of drug-excipient interactions fourier transform infrared spectroscopy**

Compatibility between drug and the polymers were studied by FTIR spectra. FTIR studies were carried out for drug and its physical mixture (1:1). The sample was dispersed in KBr powder and the pellets were made by applying 6000 kg/cm² pressure and analyzed. FTIR spectra were obtained by diffuse reflectance on a FTIR spectrophotometer type FTIR 8400 (Schimadzu Corporation, Japan). The positions of FTIR bands of important functional groups of drug were identified and were cross checked in obtained spectra.[8]

**Differential scanning calorimetry (DSC)**

DSC studies for drug and its physical mixture (1:1) were carried out using DSC-60 calorimeter (Schimadzu Corporation, Japan). The instrument was calibrated with an indium and zinc standard. The sample was heated from 10 to 300°C at a heating rate of 25°C/ min to remove thermal history. The sample was then immediately cooled to 10°C and reheated from 10 to 300°C under the flow of nitrogen at a heating rate of 10°C/minute.

**Preparation of patches**

Trandolapril transdermal patches were prepared by solvent casting technique using HPMCK4M, gantrez, eudragit and carbopol as polymers (Table 1). Glycerine and polysorbate 80 were used as plasticizer and penetration enhancer respectively. Ethanol, methanol and dichloromethane were used as solvents.

- Trandolapril (drug) was dissolved in little quantity of solvent and polymers were dissolved in remaining solvent/solvent mixture.
- Drug, polymer solutions along with plasticizer and permeation enhancer were sonicated for 30 minutes and examined for air entrapment.
- The solution was poured onto glass moulds of 10.5 cm² and air dried for overnight at room temperature. An inverted funnel was kept on the mould for controlled evaporation.

- The dried film of the drug was peeled from the mould and packed in aluminium foil and kept in desiccator till further use.

**Table 1: Composition of trandolapril patches**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F 1</td>
</tr>
<tr>
<td>Trandolapril (mg)</td>
<td>200</td>
</tr>
<tr>
<td>HPMCK4M (mg)</td>
<td>975</td>
</tr>
<tr>
<td>Gantrez (mg)</td>
<td>--</td>
</tr>
<tr>
<td>Eudragit RL 100 (mg)</td>
<td>--</td>
</tr>
<tr>
<td>Carbopol 934P (mg)</td>
<td>--</td>
</tr>
<tr>
<td>Polysorbate 80 (ml)</td>
<td>0.2</td>
</tr>
<tr>
<td>Glycerine (ml)</td>
<td>0.4</td>
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<tr>
<td>Ethanol (ml)</td>
<td>--</td>
</tr>
<tr>
<td>Methanol (ml)</td>
<td>7.5</td>
</tr>
<tr>
<td>DCM (ml)</td>
<td>7.5</td>
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</tbody>
</table>

**Thickness**

Thickness of patches was measured using a micrometer (Mitutoyo Co., Japan) for a pack of 5 films. Mean ± standard deviation was calculated[9].

**Weight Variation**

Ten patches (1 × 1 cm²) were selected and weight variation was evaluated for each formulation[10].

**Folding Endurance**

Each patch was folded repeatedly several times at the same place until the patch breaks. The first appearance of breaking was observed and then the folding endurance was reported by the number of foldings before it was broken[11].

**Loss of Moisture**

The patches were initially weighed (W1) individually and placed in a dessicator (containing activated silica) at room temperature (30 ± 0.5°C). After three days, the films were taken out and weighed (W2). Percent loss of moisture was calculated using formula, given below[12].

\[
\% \text{ Loss of Moisture} = \frac{W1 - W2}{W2} \times 100
\]

**Moisture Uptake**

The patches were weighed (W1) and placed in a
dissicator (containing 100 ml saturated solution of sodium chloride, 75% RH) at room temperature (30 ± 0.5°C). After three days, the films were removed and weighed (W2). Percent gain of moisture was calculated using the given formula[13],

\[
\% \text{ Gain of moisture} = \frac{W_1 - W_2}{W_2} \times 100
\]

**Drug Content**

Drug content of patches was determined by dissolving five patches (1 cm²) in 100 ml of 7.4 buffer. After suitable dilutions the resultant solution was filtered and analysed for trandolapril content spectrophotometrically[6,7].

**HPLC analysis**

Analysis of samples was performed using a Schimadzu 10 AVP (Japan) HPLC system equipped with UV detector and a Waters C-18 column (300 × 4.6 mm i.d) at ambient temperature. The mobile phase was mixture of phthalate buffer pH 2.8 and acetonitrile in 1:1 ratio. The solution was filtered through 0.45 μm filter and degassed by sonication. The flow rate was 1 ml per minute. The detection was carried on at 215 nm wavelength. A calibration curve was plotted for trandolapril in the range of 25–150 μg/ml. A good linear relationship was observed between the concentration of trandolapril and its peak area (r² = 0.9981). Precision and accuracy of the HPLC method were estimated[14].

**In vitro permeation studies using rat skin**

Franz diffusion cell was used for in vitro skin permeation studies. The skin of the rat abdominal region was used. The preparation of skin for diffusion study was as follows. Male wistar rats weighing 200–250 g were used. The rats were anaesthetised using chloroform and the abdomen was carefully shaved with scissors and razor[15]. Full thickness skin (i.e., epidermis, subcutaneous and dermis) was excised from the abdominal site[16]. Any skin with damages was rejected. The skin sample was placed in the Franz diffusion cell. Slightly larger skin was taken to help its fixation on the diffusion cell. The patch of area 3.14 cm² was used. The receptor compartment was filled with phosphate buffer, pH 7.4. Samples of one ml were withdrawn at predetermined time intervals and one ml was replaced with fresh solution. Required dilutions were made for the sample and the amount of drug that reached receptor compartment was analyzed for drug content using HPLC and the data was statistically analysed by one way ANOVA followed by turkey post hoc test for multiple comparison using graph pad prism. Differences were considered to be significant at a level of p < 0.05.

The permeability coefficients (P) were calculated as follows[17]:

\[
P = \frac{dQ/dt}{CA}
\]

Where

- dQ/dt - Permeation rate,
- C - Concentration of the donor chamber
- A - Surface area of diffusion

Steady state fluxes (Jss) were calculated by dividing the slope of cumulative amount permeated vs time curve by the diffusional area.

**Stability studies**

Stability studies were conducted according to the ICH Q1A (R2) guidelines. Patches were wrapped in aluminum foil and were kept in stability chamber at a temperature of 40±2ºC and 75±5% RH for 6 months[18]. Samples were withdrawn at the end of 6 months and analyzed for drug content and in vitro permeation. Zero time samples were used as control for the study and the results were statistically analyzed by using t-test and p < 0.05 were considered as significant.

**RESULTS AND DISCUSSION**

**Investigation of drug–excipient interactions—FTIR spectral analysis**

Trandolapril and its physical mixture were subjected to FTIR spectroscopic analysis. The obtained spectra are shown in Figure 1. The FTIR spectra of pure trandolapril showed sharp characteristic peaks at 1024 (C–C stretch), 1193 (C-N stretch), 1396 (Carboxylate anion stretch), 1541 (C=C stretch), 1735 (C=O stretch), 2879, 2941 (C–H stretch) and 3279 cm⁻¹ (N–H stretch). All the above characteristic peaks appeared in the spectra of physical mixture at the same wave numbers.
indicating no modification or interaction between the drug and polymers.

**Differential scanning calorimetry**

DSC studies were carried out for trandolapril pure drug and its physical mixture. DSC thermograms obtained are shown in Figure 2. The DSC thermogram of trandolapril showed an endothermic peak at 123.19°C corresponding to its melting temperature, which was also detected in the thermograms of physical mixture, signifying no interaction between trandolapril and the polymers.

**Physicochemical evaluation of trandolapril patches**

Physicochemical evaluation data was shown in Table 2. The drug content in all the patches was found to be uniform. The patches were weighing in between 26.79 mg to 29.12 mg. Patch thickness was in the range of 251 μm to 274 μm. Folding endurance of the patches was in the following order F 3>F 2>F 4>F 1. The folding endurance of all the films was optimum, films exhibited good physical and mechanical properties. The overall moisture uptake was low (~10%), which was satisfactory for the patches. Thus, the general physical properties are satisfactory.

**In vitro permeation studies**

In vitro permeation studies for the patches were carried out in triplicate and after 24 hours the release was found to be 89.12 ± 7.62, 82.82 ± 5.72, 76.77 ± 6.13 and
Table 2: Physical evaluation of trandolapril patches

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Parameter</th>
<th>% Drug content</th>
<th>Weight variation (mg)</th>
<th>Thickness (μm)</th>
<th>Folding endurance</th>
<th>Moisture Uptake (%)</th>
<th>Loss of moisture (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>% Drug content</td>
<td>3.86 ± 0.71</td>
<td>28.98</td>
<td>272 ± 1.53</td>
<td>244 ± 6.51</td>
<td>3.12 ± 1.22</td>
<td>3.23 ± 2.41</td>
</tr>
<tr>
<td>F2</td>
<td>Weight variation (mg)</td>
<td>3.88 ± 0.35</td>
<td>29.12</td>
<td>274 ± 2</td>
<td>285 ± 6</td>
<td>6.27 ± 2.51</td>
<td>4.09 ± 2.31</td>
</tr>
<tr>
<td>F3</td>
<td>Thickness (μm)</td>
<td>4.02 ± 0.17</td>
<td>27.80</td>
<td>251 ± 0.58</td>
<td>295 ± 6.5</td>
<td>1.89 ± 0.97</td>
<td>2.07 ± 1.83</td>
</tr>
<tr>
<td>F4</td>
<td>Folding endurance</td>
<td>3.97 ± 0.18</td>
<td>26.79</td>
<td>262 ± 1.16</td>
<td>267 ± 7.02</td>
<td>4.53 ± 2.43</td>
<td>3.34 ± 1.89</td>
</tr>
<tr>
<td></td>
<td>Moisture Uptake (%)</td>
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<tr>
<td></td>
<td>Loss of moisture (%)</td>
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</table>

80.28 ± 5.38% for the formulations F1, F2, F3 and F4, respectively (Fig. 3). The data of in vitro permeation was analyzed by one way ANOVA and there was no significant difference between means at 2, 3, 4 and 15 hours. F1 showed faster release due to loosely bound polymer molecules leads to faster erosion, allowing the faster release of trandolapril from the patches. F2 showed slow release of trandolapril from the patches may be due to formation of strong hydrogel by gantrez and HPMC complex. This gel acts as a barrier for drug diffusion. Formulation F4 showed moderate release due to presence of carbopol along with HPMC. Presence of eudragit in formulation F3 reduced the release of trandolapril, which may be due to the water insolubility of eudragit and the consequent lower dissolution and slower erosion of films.

In vitro permeation study formulation F1 showed a maximum release of the drug, 89.12 ± 7.62% in 24 hours (Fig. 3), and this formulation was considered as optimized one and used for further study. The order of drug release was found to be F1 > F2 > F4 > F3. The in vitro permeation profile of F1 formulation could be best expressed by Korsmeyer–Peppas model and F2, F3 and F4 formulation could be best expressed by zero order model (Table 3). All the formulations showed a...
non-Fickian release pattern as it was evidenced from the release exponent (n > 0.5). This indicates coupling of the diffusion and erosion mechanism, called anomalous diffusion and shows that the drug release is controlled by more than one process. So, the suggested drug release mechanism for trandolapril patches may be combination of diffusion and erosion of polymer matrix.

The mean steady state flux ($J_{SS}$) was found to be 0.3027 ± 0.01, 0.2924 ± 0.01, 0.2558 ± 0.01, 0.2763 ± 0.007 mg/cm²/hr and the permeability coefficient was found to be 0.0756 ± 0.003, 0.0731 ± 0.002, 0.0639 ± 0.003, 0.069 ± 0.002 cm/hr for the formulations F 1, F 2, F 3 and F 4, respectively.

**STABILITY STUDIES**

Accelerated stability studies were performed for optimized formulation (F 1) as per ICH Q1A (R2) guidelines at 40 ± 2°C and 75 ± 5% RH for 6 months. After specified duration, visual examination of the patches did not show any change in morphology. The results of the stability studies revealed that there was significant change in drug content and in vitro permeation. The cumulative percentage of trandolapril permeated in 24 hours was found to be 82.76 ± 5.91%. Flux and permeability coefficient of trandolapril was found to be 0.2744 ± 0.048 mg/cm²/hr and 0.0686 ± 0.005 cm/hr, respectively for the optimized formulation.

The in vitro permeation profile of F 1 after stability study could be best expressed by zero order model, as the plots showed highest linearity ($r^2$: 0.9941) and the obtained release exponent (n) value, 0.9845, supported non-Fickian release and it was observed that there was a change in the best fit model and no change in transport mechanism after stability study.

**CONCLUSION**

Transdermal patches of trandolapril were prepared by solvent evaporation technique. The patches exhibited good physical properties. The in vitro permeation patches was attempted using Franz diffusion cell, with and rat skin. Good results were obtained both in vitro conditions for patches. The statistical investigation of in vitro permeation data showed that the coupling of the diffusion and erosion is the mechanism of drug release. From the present investigation, it can be concluded that transdermal patches of trandolapril may provide sustained delivery for prolonged periods in the management of hypertension, which can be a good way to bypass the extensive hepatic first-pass metabolism.

**ACKNOWLEDGEMENT**

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**REFERENCES**

