Research Article

Formulation and Evaluation of Nateglinide Patches for Transdermal Drug Delivery.

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ABSTRACT

Transdermal drug delivery is an alternative route for systemic drug delivery which minimizes the absorption and increases the bioavailability. Nateglinide is an Anti-Diabetic drug with a shorter half life, low bioavailability up to 72 % undergoes extensive first pass metabolism are required to maintain the therapeutic level it has chosen as transdermal drug delivery system. The present study was to formulate and evaluate transdermal drug delivery system of Nateglinide using polymers such as HPMC & Eudragit RL100 by solvent casting technique. The prepared formulations were evaluated for different physicochemical characteristics like Weight Variation, Folding Endurance, Flatness, pH of patches, % Moisture Content, % Moisture uptake, % Elongation, % Drug Content & % Drug Release. The drug release characteristics of the formulation were studied \textit{in-vitro} by using semi-permeable membrane. The \textit{in-vitro} drug release plot has shown that the drug release followed zero order kinetics & Higuchi model, which was evidenced from the regression values. Based on the drug release and physicochemical values obtained from the formulation F\textsubscript{7} is considered as an optimized formulation which shows higher percentage of drug release (96.27±0.68 % at 14 hour) with diffusion mediated mechanism. Korsmeyer-Peppas exponential plots shows fairly linear & it is well supported by their regression coefficients values & slope value (n) were >1 which suggest that drug was released by Super Case-II transport.

KEYWORDS

Nateglinide, Transdermal Patches, Transdermal Drug Delivery, Solvent Evaporation Technique & Anti-Diabetic Patches
1. INTRODUCTION
Transdermal drug delivery has been accepted as a potential non-invasive route of drug administration, with advantages of prolonged therapeutic action[1]. For decades, utilization of skin as a route for delivering drugs has been an attracting alternative to conventional methods including injections and tablets. Its advantages include the prolonged therapeutic action, decreased side effect, easy use, avoidance of pain, withdrawal in case of side effects, safety, better patient compliance,[2] avoidance of first pass metabolism and prevention of gastrointestinal degradation[3]. Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged illness and early death. It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency, and it is often combined with insulin resistance [4].Nateglinide [N-(trans-4-isopropyl cyclohexyl carbonyl) -D-phenylalanine] is a novel, highly physiologic, mealtime glucose regulator recently approved for the treatment of type II diabetes mellitus[5]. It is an anti-diabetic drug that is quick but short acting and controls postprandial blood glucose (PBG) effectively. Nateglinide belongs to the meglitinide class of anti-diabetic drugs used to treat type 2 diabetes by stimulation of pancreatic beta cells that results in the release of proinsulin. Nateglinide immediate-release tablets are administered twice or thrice a day. A sustained release formulation of nateglinide would enable control of both PBG and FBG (fasting blood glucose) with the novel advantage of improving patient compliance by decreasing multiple drug administration and minimizing side effects [6]. Nateglinide is rapidly and completely absorbed, with maximum plasma concentrations (Cmax) occurring approximately within an hour after oral administration. It possesses low oral bioavailability (72%) due to hepatic first pass metabolism after oral administration and has a short biological half life of 1h which makes frequent dosing 30 to 180 mg in 3 to 4 times in a day necessary to maintain the drug within the therapeutic blood levels for long periods[7,8]. Hence, Nateglinide is an ideal drug candidate for transdermal drug delivery. The purpose of the present work was to develop transdermal formulation of Nateglinide which increases the patient compliance and also sustain the release of drug to improve the bioavailability by using Eudragit RL100 & HPMC as polymer.

Table 1: Different formulation batches are as follows.

<table>
<thead>
<tr>
<th>Code</th>
<th>Drug</th>
<th>Polymer</th>
<th>Plasticizer</th>
<th>Enhancer</th>
<th>Name of Solvents</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nateglinide</td>
<td>HPMC K100M</td>
<td>Eudragit RL100</td>
<td>PEG-400</td>
<td>PG:DM SO (1:1)</td>
<td>DCM: Methanol</td>
</tr>
<tr>
<td>F1</td>
<td>90.00 mg</td>
<td>200.00 mg</td>
<td>450.00 mg</td>
<td>30 % w/w</td>
<td>30 % w/w</td>
<td>1:1</td>
</tr>
<tr>
<td>F2</td>
<td>90.00 mg</td>
<td>270.71 mg</td>
<td>450.00 mg</td>
<td>30 % w/w</td>
<td>30 % w/w</td>
<td>1:1</td>
</tr>
<tr>
<td>F3</td>
<td>90.00 mg</td>
<td>250.00 mg</td>
<td>600.00 mg</td>
<td>30 % w/w</td>
<td>30 % w/w</td>
<td>1:1</td>
</tr>
<tr>
<td>F4</td>
<td>90.00 mg</td>
<td>150.00 mg</td>
<td>600.00 mg</td>
<td>30 % w/w</td>
<td>30 % w/w</td>
<td>1:1</td>
</tr>
<tr>
<td></td>
<td>mg</td>
<td>mg</td>
<td>w/w</td>
<td>1:1</td>
<td>ml</td>
<td></td>
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<td>---</td>
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</tr>
<tr>
<td>F₅</td>
<td>90.00</td>
<td>200.00</td>
<td>662.13</td>
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<td>15</td>
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<tr>
<td>F₆</td>
<td>90.00</td>
<td>150.00</td>
<td>300.00</td>
<td>30 %</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>F₇</td>
<td>90.00</td>
<td>200.00</td>
<td>237.87</td>
<td>30 %</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>F₈</td>
<td>90.00</td>
<td>250.00</td>
<td>300.00</td>
<td>30 %</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>F₉</td>
<td>90.00</td>
<td>129.29</td>
<td>450.00</td>
<td>30 %</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** 3.14 CM² Patch Contains 10 mg Nateglinide. DCM: Dichloromethane, PG: Propylene Glycol

### 2. MATERIALS AND METHODS

#### 2.1. Materials

Nateglinide was obtained as a gift sample from USV Limited (Khed, Ratnagiri, Maharashtra, India), HPMC K100M from Colorcon Asia Pvt. Ltd., (Goa, India). Eudragit RL100 (ERL100) from Evonik India Pvt. Ltd (Mumbai, India), Propylene Glycol & Polyethylene Glycol (PEG)–400 from Nulife Pharmaceutical, (Pune, India), Dimethylsulfoxide (Suresh Traders-LaBin, Pune) & Double Distilled water was used throughout the study. All other chemicals and solvents were analytical reagent grade and purchased from commercial suppliers. The results obtained were analyzed for various pharmacokinetic parameters using pk functions of Microsoft excel & GraphPad Prism (Version 5.00 GraphPad Software Inc. San Diego, California, USA).

#### 2.2. Methods

**2.2.1. Drug–Polymer Interaction Studies**

To search the possible interaction between Nateglinide and polymeric materials of the patches, infrared (IR) spectra of pure substances and their formulation (F₇) were recorded using IR Spectrophotometer (FTIR-4100 JASCO- Japan) by KBr pellet method [9,10].

**2.2.2. Preparation of Transdermal Patches**

Nateglinide loaded transdermal patches containing different ratios of HPMC K100M and Eudragit RL100 were prepared by solvent casting method. The requisite ratios of polymers were weighed and were allowed to swell for 6 h in Methanol–Dichloromethane (1:1) solvent mixture. Plasticizer such as PEG-400 & Permeation enhancer such as Propylene glycol & Dimethylsulfoxide (DMSO) was incorporated at 30% w/w of polymer dry weight. Calculated amount of Nateglinide was mixed with homogenous polymer solution and poured into aluminum foil wrapped glass ring as mold (28.26 cm²). A funnel was placed over the mould in inverted position to control the rate of evaporation. The casting solvent mixture was allowed to evaporate overnight at room temperature. The dried patches were cut into required size (3.14 cm²) and wrapped in aluminum foil. Then, these Patches were kept in desiccator containing saturated solution of CaCl₂ as desiccant, at room temperature prior to use [11, 12].
2.3. Experimental Design

A response surface type Central Composite Design was employed using Design-Expert Software (Version 7.0.0 Stat-Ease Inc., Minneapolis, USA). Independent factors are HPMC K100M (X1) and Eudragit RL100(X2) concentrations at three levels [13, 14]. Weight Variation, Folding Endurance, Flatness, pH of patches, % Moisture Content, % Moisture uptake, % Elongation, % Drug Content & % Drug Release after 14 hours were kept as dependent variables [13, 14]. The different formulation of Nateglinide Transdermal Patches is as shown in Table-1.

2.4. Evaluation of Transdermal Patches

2.4.1. Weight Variation

Prepared patches were cut into 3.14 cm² pieces and weight of each patch was determined by using digital balance. The average weight of each patch and standard deviations were calculated [15, 16].

2.4.2. Folding Endurance

A strip of Patch of specific surface area (2 cm²) was cut and folded repeatedly at one place till it broke. The number of times the patch was folded before breaking at the same place represented folding endurance [17, 18].

2.4.3. Flatness

Longitudinal strips were cut out from the prepared patch, the length of each strip was measured, and then variation in the length due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips, and a 0% constriction was considered to be 100% flatness [19, 20].

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

Where, \( L_1 \) = Initial length of each strips and \( L_2 \) = Final length of each strips.

2.4.4. Surface pH

For the determination of surface pH three patches of each formulation were allowed to swell for 2 hrs in a Petridis containing 5 ml of phosphate buffer pH 7.4[21]. The surface pH was measured by pH paper placed on the surface of patches and allowed to equilibrate for 1 min. The average of the three readings was recorded [22].

2.4.5. Percentage of Moisture Content

The prepared patches were weighed and kept in desiccator containing activated silica at room temperature for 24 h. The individual patches were weighed on every alternate day until a constant weight was achieved. The percentage of moisture content was calculated by determining the difference between initial and final weight with respect to final weight [23-25].

\[ \text{Moisture Content} \, (\%) = \frac{W_1 - W_2}{W_2} \times 100 \]

Where, \( W_1 \) = Initial weight of each patch and \( W_2 \) = Final weight of each patch

Moisture Uptake

Nateglinide Transdermal patches were weighed and placed in desiccators containing a saturated solution of sodium chloride at 74% relative humidity (RH). After first week, the patches were taken out and weighed. The percentage of Water Absorptive Capacity (Moisture Uptake) was calculated as the difference between the final and initial weight with respect to the initial weight [26, 27].

\[ \text{Moisture Uptake} \, (\%) = \frac{W_2 - W_1}{W_1} \times 100 \]
Where, \( W_1 \) = Initial weight of each patch and \( W_2 \) = Final weight of each patch

2.4.6. Percentage of Elongation

Elongation of the Patches was determined by Texture Analyzer (Brookfield-CT3-10KG). Rectangular strips of 40mm × 30mm were fixed in such a way that the length of patch between the jaws. The percentage elongation was determined by noting the length just before the break point and substituted in the following Equation [28, 29].

\[
\text{Elongation (\%)} = \frac{L_1 - L_2}{L_2} \times 100
\]

Where, \( L_1 \) = Final length of each strips and \( L_2 \) = Initial length of each strips.

2.4.7. Determination of Drug Content

Formulated drug-loaded Patches were evaluated for uniformity of drug content. Strips of 3.14 cm\(^2\) from each formulation were randomly selected and transferred into a 100 ml volumetric flask containing pH 7.4 phosphate buffer and Methanol. The flask was stirred for 4 h on magnetic stirrer [30]. A blank was similarly prepared using a drug-free Patch. The obtained solutions were filtered through a 0.45 \( \mu \)m membrane. The drug content was then determined after proper dilution by UV spectrophotometer at 221 nm (JASCO V-630, Japan) [31].

2.4.8. In Vitro Drug Release Study

Drug release studies were performed with freshly prepared patches in Franz diffusion cells with volume of 27 ml and a diffusion area of 4.90 cm\(^2\). The receptor compartment contained pH 7.4 Phosphate Buffer at 37\(^\circ\)C (corresponding to 32\(^\circ\)C at the release interface) and was stirred at 50 rpm with a magnetic stirrer. Circular patches (diameter: 2.00 cm, patch thickness: approximately 0.21 mm to 0.25 mm) were centrally attached to circular piece of cellulose acetate membrane with a diameter of 2.5 cm. The cellulose acetate membrane was mounted between the donor and receptor compartment of the diffusion cell. The 1 ml samples were withdrawn at different time intervals and an equal amount of phosphate buffer, pH 7.4 was replaced each time. Absorbance of the samples were measured spectrophotometrically at 221 nm taking phosphate buffer solution, pH 7.4, as blank. The experiment was performed in triplicates and the mean values were calculated [32-35].

3. RESULTS AND DISCUSSION

3.1. Drug–Polymer Interaction Studies

The incompatibility between the Drug and Excipients were studied by FTIR spectroscopy. The spectral data of pure Nateglinide, HPMC, ERL100 and Nateglinide Transdermal Patch (F7) are presented in Fig.01-04. The results indicate that there was no chemical incompatibility between drug and excipients used in formulation.
Fig: 1: FTIR spectra of Nateglinide

Fig: 2: FTIR spectra of HPMC K100M

Fig: 3: FTIR spectra of Eudragit RL100
Fig: 4: FTIR spectra of Nateglinide Transdermal Patch (F7)

3.2. Weight Variation
The weight of patches ranged between 120 ± 1.528 mg and 144 ± 2.646 mg, which indicates that different batches patch weights, were relatively similar. The individual weights of patches within the same formulation varied only slightly as shown by the low standard deviations. The average weight of the Patches increased with increased concentration of the polymers used in producing the Patches as shown in Table 2 [36].

3.3. Folding Endurance
The values of folding endurance were found to vary from 293±4.583 to 340±3.606 which indicates good strength and elasticity. The folding endurance test results (Table-2) showed that the Patches prepared from all formulations which shows that transdermal patches were more flexible and durable.

These results demonstrated the sturdiness of the patches in maintaining their integrity with general skin folding when applied.

Table: 2- Physicochemical Properties of Nateglinide Transdermal Patches.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight Variation (mg)</th>
<th>Folding Endurance (%)</th>
<th>Flatness (%)</th>
<th>Surface pH</th>
<th>MC (%)</th>
<th>MU (%)</th>
<th>Elongation (%)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>135±1.528</td>
<td>314±5.5</td>
<td>100.08</td>
<td>6.33±1.1</td>
<td>5.72±0.5</td>
<td>10.09</td>
<td>42.50±2.6</td>
<td>99.27±1.23</td>
</tr>
<tr>
<td>F2</td>
<td>137±0.577</td>
<td>320±5.13</td>
<td>99.16±0.2</td>
<td>6.00±1.0</td>
<td>8.15±0.6</td>
<td>15.53</td>
<td>37.50±2.6</td>
<td>98.96±1.23</td>
</tr>
<tr>
<td>F3</td>
<td>142±2.00</td>
<td>332±4.00</td>
<td>100.08</td>
<td>5.63±0.5</td>
<td>7.79±0.5</td>
<td>14.09</td>
<td>58.33±1.4</td>
<td>99.12±1.43</td>
</tr>
<tr>
<td>F4</td>
<td>139±1.00</td>
<td>324±3.60</td>
<td>99.91±0.1</td>
<td>6.33±0.5</td>
<td>4.31±0.5</td>
<td>7.23±0.4</td>
<td>51.66±1.3</td>
<td>99.07±1.31</td>
</tr>
<tr>
<td>F5</td>
<td>144±2.646</td>
<td>340±3.60</td>
<td>99.08±0.6</td>
<td>6.33±0.5</td>
<td>6.08±0.6</td>
<td>11.23</td>
<td>65.00±2.0</td>
<td>99.17±0.32</td>
</tr>
</tbody>
</table>
3.4. Flatness
Flatness (%) of these patch formulations were found satisfactory, which ranged between 99.08 ± 1.37 and 100.08±0.28 % (Table 2). The results of the flatness study showed that the formulation Patches have a negligible change in the length along the longitudinally cut edges, indicating a near 100% flatness. The patches from all tested formulations appeared to have a smooth, flat surface and that smooth surface could be maintained when the patch was applied to the skin without any visible signs of constriction [37].

3.5. Surface pH
For a dermatological preparation to be safe and non-irritant its pH must be between 4 and 7 [38]. Surface pH was mainly done to know whether the patch is acidic or basic. Irritation will persist if the Patch is more acidic or basic. Surface pH of the transdermal patches was in between 5.33±0.57 and 6.33±1.15 (Table-2) which match to the pH of the skin, infers that the patch is non-irritant & desirable property [39].

3.6. Moisture Content & Moisture uptake
The % moisture content in the patches ranged from 3.36±0.21 to 8.15±0.02. The % moisture uptake in the formulations was in the range of 6.42±0.21 to 15.53±0.09 (Table-II). Moisture content and moisture uptake studies provide information regarding stability of the formulation [40]. The results revealed that the moisture content and moisture uptake were found to increase with increasing concentration of hydrophilic polymer (HPMC) [41]. The low level of moisture content in the formulation helps them to remain stable and from being a completely dried and brittle films and low moisture uptake protects the material from microbial contamination and bulkiness of the patches [42].

3.7. Percentage of Elongation
Percentage Elongation at break of the formulations prepared from combination HPMC K100M & ERL100 at different ratios which ranged between 22.50±2.50 % to 65.00±2.50 % (Table-2). The prepared patches were also found to be strong enough & provide good mechanical properties. It was also observed that the percentage elongation at break values increased with increasing concentration of ERL100 polymer [28, 43].

3.8. Drug Content
The drug content (%) in all prepared formulations varied between the range 98.75±0.41 % to 99.48±0.32 %. This indicates that the drug distribution ensures the uniform reproducible drug

<table>
<thead>
<tr>
<th></th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>F6</td>
<td>296±4.35</td>
<td>293±4.58</td>
<td>304±3.51</td>
<td>308±3.21</td>
</tr>
<tr>
<td>F7</td>
<td>124±2.08</td>
<td>120±1.52</td>
<td>129±2.08</td>
<td>132±1.52</td>
</tr>
<tr>
<td>F8</td>
<td>99.250</td>
<td>100.08</td>
<td>100.08</td>
<td>99.83</td>
</tr>
<tr>
<td>F9</td>
<td>5.76±0.5</td>
<td>6.33±0.5</td>
<td>6.33±0.5</td>
<td>5.33±0.5</td>
</tr>
<tr>
<td>F10</td>
<td>5.76±0.5</td>
<td>6.33±0.5</td>
<td>6.33±0.5</td>
<td>5.33±0.5</td>
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<tr>
<td>F11</td>
<td>5.76±0.5</td>
<td>6.33±0.5</td>
<td>6.33±0.5</td>
<td>5.33±0.5</td>
</tr>
</tbody>
</table>

*All values are expressed as mean ± SD (n = 3). MC: Moisture content & MU: Moisture uptake
release from the patch [31] Uniformity of drug distribution throughout the patch was proved by the low value of SD (Table-2).

3.9. In Vitro Drug Release

The in vitro drug release pattern of Nateglinide from formulated transdermal patches is shown in Fig. : 05-08. All these transdermal patches slowly released the drug, incorporated and sustained over a period of 14 h. The drug release from transdermal patches varied with respect to the polymer composition and nature. An increase in drug release from the transdermal patches was found with increasing concentration of polymers that are more hydrophilic in nature [44, 45]. Among all formulations, the maximum in vitro drug release (96.27±0.68%) over a period of 14 h was observed in the case of formulation No. F7, while the minimum in vitro drug release (72.37±0.49 %) over a period of 14 h was found in the case of formulation No. F5 which shows that the concentration of Eudragit RL100 increases and decreases the drug release.

The in vitro Nateglinide release data from transdermal patches were evaluated kinetically using various mathematical models like zero-order, first order, Higuchi, and Koresmeyer–Peppas. The results of curve fitting into these above mentioned models (Figure: 05-08) indicates the drug release behaviour from these formulated transdermal patches of Nateglinide at 14 h (Table-3). When the release rate of Nateglinide and their respective correlation coefficients were compared, it was found to followed zero-order kinetic (R²=0.996 to 0.999), First Order (0.832 to 0.969) and Higuchi models (R²=0.999 to 0.999) (Table-III). In order to understand the mechanism of drug release, in vitro release data were treated to kinetic models and linearity was observed with respect to zero-order kinetic & Higuchi equation. As indicated by higher values R², the drug release from all the formulations follows Zero-order drug release and Higuchi model. Therefore it was confirmed as zero-order kinetic & Higuchi model and the mechanism was found to be sustained release diffusion mediated. The above formulations treated for Korsmeyer-Peppas exponential plots (fig.08) were found to be fairly linear & it is well supported by their regression coefficients values (0.868 to 0.903) (Table 3). The slope value (n) were also calculated & they are >1(Table 3) which suggest that drug was released by Super Case-II transport.

Table 3: In Vitro drug Release of Nateglinide Transdermal Patches.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>% Drug Release after 14 hrs*</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Higuchi’s</th>
<th>Korsmeyer-Peppa’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>85.19±0.11</td>
<td>0.997</td>
<td>0.9415</td>
<td>0.997</td>
<td>0.8891</td>
</tr>
<tr>
<td>F2</td>
<td>88.21±0.21</td>
<td>0.999</td>
<td>0.9356</td>
<td>0.999</td>
<td>0.8780</td>
</tr>
<tr>
<td>F3</td>
<td>74.47±1.07</td>
<td>0.999</td>
<td>0.9672</td>
<td>0.999</td>
<td>0.8981</td>
</tr>
<tr>
<td>F4</td>
<td>79.38±0.31</td>
<td>0.998</td>
<td>0.9446</td>
<td>0.998</td>
<td>0.9031</td>
</tr>
<tr>
<td>F5</td>
<td>72.37±0.49</td>
<td>0.999</td>
<td>0.9696</td>
<td>0.999</td>
<td>0.9004</td>
</tr>
<tr>
<td>F6</td>
<td>93.54±0.26</td>
<td>0.999</td>
<td>0.8956</td>
<td>0.999</td>
<td>0.8850</td>
</tr>
<tr>
<td>F7</td>
<td>96.27±0.68</td>
<td>0.999</td>
<td>0.8327</td>
<td>0.999</td>
<td>0.8842</td>
</tr>
<tr>
<td>F8</td>
<td>91.33±0.42</td>
<td>0.996</td>
<td>0.9368</td>
<td>0.996</td>
<td>0.8680</td>
</tr>
<tr>
<td>F9</td>
<td>83.97±0.21</td>
<td>0.999</td>
<td>0.9436</td>
<td>0.998</td>
<td>0.8917</td>
</tr>
</tbody>
</table>

*All values are expressed as mean ± SD (n = 3).
Fig. 5: Zero Order Plots for Nateglinide Transdermal Patches

Fig. 6: First Order plots for Nateglinide Transdermal Patches
4. CONCLUSION
Transdermal patches of Nateglinide using polymers like HPMC and ERL100 in various proportions and combinations showed satisfactory physicochemical characteristics. The proportional amounts of various hydrophilic polymers in various formulations have influence on drug release from these formulated Nateglinide transdermal patches. From the present study it
can be concluded that, Transdermal drug delivery system for Nateglinide with HPMC K100M and Eudragit RL 100 meet the ideal requirement for Transdermal devices which can be good way to bypass the extensive hepatic first pass metabolism and increase bioavailability. Transdermal patches of Nateglinide may provide sustained transdermal delivery for prolonged periods in the therapy of Diabetics, which can be HPMC and ERL100 of moderate level useful for preparation of sustained release matrix transdermal patch formulation.

5. CONFLICT OF INTEREST
The authors declare that there is no conflict of interests regarding the publication of this paper.

6. REFERENCES


