FORMULATION DEVELOPMENT AND CHARACTERIZATION OF TRANSDERMAL FILM OF NISOLDIPINE

K.D. Dhondge1*, D.M. Patil1, A.A. Phatak2, D.S. Pachpute1

1Department of pharmaceutics, KBHSS Trust’s Institute of Pharmacy, Malegaon Camp, Malegaon 423103
2Department of pharmaceutics, Modern College of Pharmacy, Nigadi, Pimpri, Chinchwad, 411044, Pune.

ABSTRACT
Nisoldipine is a second generation dihydropyridine calcium antagonist and used in the treatment of stable angina and arterial hypertension. Extensive first pass metabolism, low bioavailability (5%) altogether makes it an ideal candidate for transdermal drug delivery. The objectives of this study were to develop matrix-type transdermal patches of nisoldipine. Polymeric films of nisoldipine were prepared by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers were studied by infrared spectroscopic and differential scanning calorimetric studies. Transdermal patches were prepared with different ratios of combination of polymers like HPMC:EC, HPMC: PVP. They were evaluated for physicochemical parameter in vitro release of the drug from the films followed anomalous transport (0.5 < n < 1). The permeation studies were performed using Franz-type diffusion cells. The effect of the polymers on the drug release, percentage moisture content, percentage moisture uptake, folding endurance, and thickness, were investigated. In vitro release of the drug from the films followed anomalous transport (0.5 < n < 1) from all the patches, In vitro release profiles showed that the release of the drug was sustained and it extended over a period of 24 hr. Formulation F1 was considered as the best formulation with maximum drug release of 95.69%.

KEYWORDS: Transdermal, Nisoldipine, Polymeric film, In vitro release.

INTRODUCTION
Transdermal drug delivery system is defined as the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate. Transdermal patches are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effect of drug. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver the drug via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time.1,2

Transdermal delivery systems are classified in different categories, according to the technological basis of their approach, including the membrane permeation-controlled and
thematrix diffusion-controlled transdermal therapeutic systems. Polymer matrices make good reservoirs for sustained release medications.\[^3\]

Recently, it is becoming evident that the benefits of i.v. drug infusion can be closely duplicated, without its hazards, by using the skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation. The oral route of administration has certain disadvantages such as destruction of drugs by hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract. Continuous intravenous administration at a programmed rate has been recognized as a superior mode of drug delivery not only to bypass hepatic first pass effect, but also to maintain a constant, prolonged and therapeutically effective drug level in the body.\[^4,5\]

**MATERIALS AND METHODS**

Nisoldipine was purchased from sigma drug laboratory Pvt. Ltd., HPMC K-15M, PVP K-30 and EC was provided as gift sample by Ipca lab, Mumbai. Ethanol and chloroform of analytical grade was purchased from Vishal chemicals, Mumbai.

**Methods**

The section is instantiated and materialized by a set of methods, techniques and tools. It covers procedure, pre and post formulation characterization of TDDS.

**Preformulation studies**

The study involves the development of analytical technique and the curve of linearity, revise of solubility profile of the Nisoldipine, and the incompatibility profile between the drug and the polymer of choice.

**Development of analytical method by UV spectroscopy**

The UV spectroscopic analytical method was developed to characterize and estimate the drug in and out of dosage form throughout the entire work. The principle involved in the method was absorption of UV light by the drug moiety. The method was developed using Shimadzu 1800 as the system and UV Probe as the software.

**Curve of Linearity**

For development of analytical curve the drug was dissolved in small amount of ethanol and volume was made up to 100ml with pH 7.4 phosphate buffer to get 100μg/ml solution of Nisoldipine. The further dilutions of the same were made with phosphate buffer pH 7.4 to get a range of concentrations 5, 10, 15, 20, 25, 30 and 35 mcg/ml respectively and analysed by UV-Spectroscopy.

**Incompatibility study**

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The drug polymer interaction study was carried out by Fourier-Transfer infra-red spectrum analysis. The FTIR spectra’s of dry samples maintained at isothermal stress conditions were recorded on Shimadzu FTIR 8400S. The KBr pellet method was employed as FTIR sampling technique. The samples – pure drug and the physical blend of drug and polymers stored at isothermal stress condition were mixed with KBr (IR grade) at ratio of 1:5 by weight. Thinlayered pellets were prepared by subjecting samples to hydraulic press 10,000-12,000 kg/cm² pressure. The analysis was carried in the frequency range between 4,000-400 cm⁻¹ with 4 cm⁻¹ resolution. The results were the mean of 6 scans.

**Formulation of transdermal film of Nisoldipine**

Transdermal patches of Nisoldipine were prepared by solvent evaporation technique for the formulation shown. The required amount of polymers was accurately weighed and dissolved in the solvent 5 ml of chloroform and kept aside to form a clear solution. DBT (30%) was used as a plasticizer and different permeation enhancer DMSO (10%). 20 mg of Nisoldipine (drug) was dissolved in 5 ml ethanol, slowly added in polymer solution and mixed thoroughly to obtain a uniform solution. The resulted uniform solution was poured in a Petri plate and dried. A funnel was placed over the Petri plate to prevent fast evaporation of the solvent. After 24 hrs the dried films were taken out and stored in desiccators for further studies.

**Evaluation of transdermal patches.**

**Thickness of patch.**

The thickness of patch was measured by digital vernier calliper. The thickness uniformity was measured at three different sites and average of three readings was taken with standard deviation.

**Weight Variation test.**

The three disks of 2 cm × 2 cm (4 cm²) was cut and weighed on electronic balance for weight Variation test. The test was done to check the uniformity of weight and thus the batch-to-batch variation.

**Tensile Strength.**

Tensile strength of the film was checked by Universal Tensile Strength Testing Machine (LS5, Lloyd Instruments Limited, UK) equipped with a 500 N load cell. Test was conducted under normal laboratory conditions. The film of 4 cm² was randomly selected and ASTM D-882 method was used to perform the test. The lower clamp was held stationary and the film was pulled apart by the upper clamp at a speed of 50 mm/min. The force of the film at the point, when the film broke was recorded. NexygenPlus3 software was used for data collection and
performance of calculations. The experiment was performed in triplicate, and average values were reported.

The tensile strength at break value was calculated using formula:

\[
\text{Tensile strength} = \frac{\text{force at break (N)}}{\text{Initial cross sectional area (mm}^2\text{)}} \quad \ldots \ldots \quad (1)
\]

**Percent elongation.**\(^{[9]}\)

When stress is applied, a strip sample stretches referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample

\[
\% \text{ elongation} = \frac{\text{Increase in length of strip}}{\text{Initial length of strip}} \times 100 \quad \ldots \ldots \quad (2)
\]

**Percentage moisture content.**\(^{[8,9]}\)

The prepared patches were marked, then individually weighed and kept in a vacuum desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patch were individually weighed until they showed a constant weight. The Percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

\[
\% \text{ of moisture content} = \frac{(X-Y)}{Y} \times 100
\]

Where, \(X = \text{Initial weight}, Y = \text{Final weight}\)

**Percentage moisture uptake.**\(^{[8,9]}\)

The weighed patches were kept for drying in vacuum desiccator at normal room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the patch were reweighed until they showed a constant weight. The Percentage moisture uptake was calculated from the below mentioned formula.

\[
\% \text{ of moisture uptake} = \frac{(Y-X)}{X} \times 100
\]

Where, \(x = \text{Initial weight}, Y = \text{Final weight}\)

**Folding endurance.**\(^{[6,10]}\)

The folding endurance was expressed as the number of folds (number of times of patch was folded at the same plain) required breaking any polymeric patch or developing visible cracks. This gives an indication of brittleness of the film. A small strip of 4 cm\(^2\) square cm was subjected to this test by folding the film at the same place repeatedly several times until a visible crack was observed.

**Drug content uniformity.**\(^{[11,12]}\)
The patch of area 2 cm × 2 cm (4 cm$^2$) was cut and dissolved in 5 ml of ethanol and volume was made up to 100 ml with phosphate buffer pH 7.4 and shaken for 6 hrs. The solution filtered through a filter medium. The absorbance of the solution was measured at 238 nm.

**In vitro diffusion studies**

The diffusion study was carried out by using Franz diffusion cell. In this method egg membrane is used as the model membrane. The membrane was placed between the donor compartment and the reservoir compartment (phosphate buffer PH 7.4). The patch was placed on the membrane and the compartments clamped together. The receptor compartment (20 ml capacity) was filled with phosphate buffer PH 7.4 and hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. 1 ml of sample withdrawn and replaced with receptor medium. 1 ml sample was diluted up to 5 ml with phosphate buffer 7.4 to get concentration in between 5-35 μg/ml and assayed spectrophotometrically at 238 nm and amount of drug release at various time intervals was calculated.$^{[12,13]}$

**RESULTS & DISCUSSION**

**Thickness of patch**

The thickness of the prepared patches (F1-F3) with different combination of polymers (HPMC: PVP) varied from 0.189 mm to 0.211 mm respectively and HPMC: EC ratio of polymeric films were ranged from 0.161 mm to 0.233 mm respectively. The results indicated that the film thickness measurement ensured uniformity of the patches prepared by solvent evaporation technique. The results were shown in the Table II.

**Weight Variation test**

The weight of the prepared patches (F1-F3) with different combination of polymers (HPMC: PVP) ranged from 254 ± 0.57 mg to 264 ± 0.57 mg and 248 ± 0.57 mg to 257 ± 0.57 mg for (F4-F6) HPMC/EC. The results were shown in Table II. Thus, it was concluded that the process adopted for casting the films in this investigation was capable of giving uniform drug content and minimum intra batch variability.

**Tensile Strength**

The mean value was found to vary between 203.33 ± 5.03 - 173.66 ± 1.52 g/cm$^2$. The tensile strength of patches was found to be in the following order F1 > F6 > F2 > F5 > F3 > F4. These results indicated that increasing the concentration of hydrophilic polymer increased the tensile strength. The polymers such as HPMC and PVP were stable and possessed good film making characters. The polymers have been used successfully in the design of various patches.

**Percent elongation test**
The mean value was found to vary between $83.69 \pm 0.48$ to $111.48 \pm 0.57$. These results indicated that increasing the concentration of hydrophilic polymer decreased the percent elongation. The polymers such as HPMC, EC and PVP were stable and possessed good film making characters.

**Percentage moisture content**

The results of moisture content studies were shown in Table II. The results indicated that the hydrophilic polymers are directly proportional to the percentage of moisture contents. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long-term storage. The low moisture absorption protects the material from microbial contamination and bulkiness of the patches.

**Percentage moisture uptake**

The result showed that moisture uptake was found to be maximum for formulation F3 ($1.543 \pm 0.12$) whereas moisture uptake observed to be minimum for formulation F6 ($1.315 \pm 0.10$). The water absorption capacity was found to be more for hydrophilic polymer HPMC, PVP than lipophilic polymers EC. The moisture uptake provides information regarding the stability of the formulation, conversely moisture absorbed did not affect film strength and the integrity.

**Folding endurance**

The folding endurance is measurement of the ability of the patch to withstand the rupture while handling. Folding endurance was in the range $54.33 \pm 0.57$ to $72 \pm 1.00$. The films were folded maximum of 72 times in the formulation F3 until the film cracks, which was taken as end point and minimum of 54 folds in the formulation F6. The results were shown in the Table II. The folding endurance decreased with increasing concentration of ethyl cellulose polymers. The folding endurance of PVP patches was higher than patches containing HPMC, EC polymers. The polymers such as PVP and HPMC were stable, possess good film making characters. The polymers have been used successfully in the design of various patches.

**Drug content uniformity**

The result showed that the drug content of the transdermal patches was ranges from $90.20\%$ to $95.43\%$. The result showed that drug content was found to be maximum for formulation F1 (95.43) whereas drug content observed to be minimum for formulation F5 (90.20). This indicates minimum batch variability, which demonstrates homogenous distribution of the drug and thus, gives assurance of the strength of slow dose drugs.

**Diffusion studies**

Formulation (F1-F3) prepared using different combination of polymers (HPMC: PVP) shows the cumulative % drug release 79.93%, 80.22%, 95.69%. Formulation (HPMC: EC) shows the
cumulative % drug release 76.66%, 84.93%, 94.49%, at the end of 24 hrs. It was observed that the drug release was found to increase on increasing the concentration of hydrophilic polymers F1 and F4 shows better drug release in 24hrs.

**Analysis of the Release Mechanism**

Drug release process was not zero order or first order in nature. To find out exact mechanism, drug release data of all formulations were fitted in Higuchi & Korsmeyer - Peppas equation. All the formulations in this study were best expressed by Higuchi’s classical diffusion equation, as the plots showed high linearity. The linearity of the equation indicated that the release approximates fickian diffusion mechanism.

**Table I: Formulation of Nisoldipine transdermal patches**

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug (mg)</th>
<th>HPMC K15 (mg)</th>
<th>PVP K-30</th>
<th>EC</th>
<th>Plasticizer (%)</th>
<th>Permeation enhancer (%)</th>
<th>Solvent 10ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>20</td>
<td>300</td>
<td>100</td>
<td>--</td>
<td>DBT (30%)</td>
<td>DMSO (10%)</td>
<td>Chloroform:Ethanol</td>
</tr>
<tr>
<td>F2</td>
<td>20</td>
<td>200</td>
<td>200</td>
<td>--</td>
<td>DBT (30%)</td>
<td>DMSO (10%)</td>
<td>Chloroform:Ethanol</td>
</tr>
<tr>
<td>F3</td>
<td>20</td>
<td>100</td>
<td>300</td>
<td>--</td>
<td>DBT (30%)</td>
<td>DMSO (10%)</td>
<td>Chloroform:Ethanol</td>
</tr>
<tr>
<td>F4</td>
<td>20</td>
<td>300</td>
<td>--</td>
<td>100</td>
<td>DBT (30%)</td>
<td>DMSO (10%)</td>
<td>Chloroform:Ethanol</td>
</tr>
<tr>
<td>F5</td>
<td>20</td>
<td>200</td>
<td>--</td>
<td>200</td>
<td>DBT (30%)</td>
<td>DMSO (10%)</td>
<td>Chloroform:Ethanol</td>
</tr>
<tr>
<td>F6</td>
<td>20</td>
<td>100</td>
<td>--</td>
<td>300</td>
<td>DBT (30%)</td>
<td>DMSO (10%)</td>
<td>Chloroform:Ethanol</td>
</tr>
</tbody>
</table>

**Table II: Physicochemical evaluations of Nisoldipine transdermal patches**

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Thickness (mm)</th>
<th>Weight variation (mg)</th>
<th>Folding Endurance</th>
<th>Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.211 ± 0.0015</td>
<td>254 ± 0.57</td>
<td>65.33 ± 1.00</td>
<td>95.43 ± 0.16</td>
</tr>
<tr>
<td>F2</td>
<td>0.191 ± 0.0011</td>
<td>258 ± 0.57</td>
<td>67.66 ± 1.00</td>
<td>90.39 ± 0.28</td>
</tr>
<tr>
<td>F3</td>
<td>0.189 ± 0.0005</td>
<td>264 ± 0.57</td>
<td>72.66 ± 1.00</td>
<td>90.76 ± 0.15</td>
</tr>
<tr>
<td>F4</td>
<td>0.161 ± 0.007</td>
<td>257 ± 0.57</td>
<td>64.66 ± 0.57</td>
<td>93.08 ± 0.16</td>
</tr>
<tr>
<td>F5</td>
<td>0.171 ± 0.0013</td>
<td>253 ± 0.57</td>
<td>57.66 ± 0.57</td>
<td>90.20 ± 0.16</td>
</tr>
<tr>
<td>F6</td>
<td>0.223 ± 0.0016</td>
<td>248 ± 0.57</td>
<td>54.33 ± 0.57</td>
<td>91.03 ± 0.16</td>
</tr>
</tbody>
</table>

*All values are expressed as Mean ±SD, n = 3*
### Table III: Moisture content, uptake, tensile strength & % elongation recovered for Nisoldipine patches

<table>
<thead>
<tr>
<th>Formulations</th>
<th>% Moisture content</th>
<th>% Moisture uptake</th>
<th>Tensile strength</th>
<th>% Elongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1.704 ± 0.179</td>
<td>1.357 ± 0.15</td>
<td>203.33 ± 5.03</td>
<td>83.69 ± 0.48</td>
</tr>
<tr>
<td>F2</td>
<td>1.643 ± 0.504</td>
<td>1.483 ± 0.33</td>
<td>195.66 ± 2.51</td>
<td>94.15 ± 0.98</td>
</tr>
<tr>
<td>F3</td>
<td>1.532 ± 0.309</td>
<td>1.543 ± 0.12</td>
<td>183.66 ± 2.08</td>
<td>111.48 ± 0.57</td>
</tr>
<tr>
<td>F4</td>
<td>1.665 ± 0.285</td>
<td>1.432 ± 0.22</td>
<td>173.66 ± 1.52</td>
<td>75.2 ± 0.20</td>
</tr>
<tr>
<td>F5</td>
<td>1.607 ± 0.142</td>
<td>1.410 ± 0.20</td>
<td>184.66 ± 2.51</td>
<td>93.8 ± 0.55</td>
</tr>
<tr>
<td>F6</td>
<td>1.471 ± 0.101</td>
<td>1.315 ± 0.10</td>
<td>195.67 ± 2.51</td>
<td>102.4 ± 1.05</td>
</tr>
</tbody>
</table>

*All values are expressed as Mean ±SD, n = 3

### Table IV: Cumulative Percentage Drug release of Nisoldipine from F1-F6 formulations.

<table>
<thead>
<tr>
<th>TIME (hrs)</th>
<th>Percentage cumulative drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>1</td>
<td>9.78±0.04</td>
</tr>
<tr>
<td>2</td>
<td>20.95±0.03</td>
</tr>
<tr>
<td>3</td>
<td>27.95±0.03</td>
</tr>
<tr>
<td>4</td>
<td>35.02±0.03</td>
</tr>
<tr>
<td>5</td>
<td>39.11±0.05</td>
</tr>
<tr>
<td>6</td>
<td>44.29±0.03</td>
</tr>
<tr>
<td>8</td>
<td>55.05±0.04</td>
</tr>
<tr>
<td>10</td>
<td>62.65±0.04</td>
</tr>
<tr>
<td>12</td>
<td>70.77±0.04</td>
</tr>
<tr>
<td>24</td>
<td>95.69±0.04</td>
</tr>
</tbody>
</table>

*All values are expressed as Mean ±SD, n = 3*
Table V: Release kinetic data of Nisoldipine containing matrix type of F1-F6.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Mathematical Models</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero order (r2)</td>
<td>First order (r2)</td>
<td>Higuchi (r2)</td>
<td>Korsmeyer Pappas Model (r2)</td>
<td>n</td>
</tr>
<tr>
<td>F1</td>
<td>0.884</td>
<td>0.449</td>
<td>0.996</td>
<td>0.738</td>
<td>0.356</td>
</tr>
<tr>
<td>F2</td>
<td>0.884</td>
<td>0.453</td>
<td>0.998</td>
<td>0.774</td>
<td>0.320</td>
</tr>
<tr>
<td>F3</td>
<td>0.878</td>
<td>0.478</td>
<td>0.978</td>
<td>0.766</td>
<td>0.290</td>
</tr>
<tr>
<td>F4</td>
<td>0.882</td>
<td>0.468</td>
<td>0.980</td>
<td>0.768</td>
<td>0.339</td>
</tr>
<tr>
<td>F5</td>
<td>0.874</td>
<td>0.474</td>
<td>0.978</td>
<td>0.772</td>
<td>0.281</td>
</tr>
<tr>
<td>F6</td>
<td>0.901</td>
<td>0.485</td>
<td>0.982</td>
<td>0.774</td>
<td>0.281</td>
</tr>
</tbody>
</table>

Figure I: *In-vitro* release profile of Nisoldipine transdermal patches (F1 – F3)

Figure II: *In-vitro* release profile of Nisoldipine transdermal patches (F4 – F6)
CONCLUSION

From the above experiment it can be concluded that the transdermal film of Nisoldipine could be formulated successfully by using different combination of polymers. Formulation F1 and F4 shows better results for Tensile strength, Percent elongation, moisture content, moisture uptake and in-vitro diffusion for 24 hr (i.e. 95.69%, 94.49%) It was observed that the increase in the concentration of hydrophilic polymers increases the % drug release. All the formulations in this study were best expressed by Higuchi’s classical diffusion equation. To confirm the diffusion mechanism, the data were fitted to Korsmeyer-Peppas model. The n values for formulations ranged from 0.281 to 0.356, indicating that the release mechanism was Fickian.

REFERENCES


For Correspondence
Kavita D. Dhondge
Email: kavitaddhondge@gmail.com