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Original Article

# Formulation and Evaluation of Nitrendipine Loaded Transdermal Patch Using HPMC K-15 and Eudragit RS100 Polymers

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ABSTRACT

Nitrendipine is an antihypertensive agent, classified under calcium channel blocker shows marked vasodilator action. The aim of the present work is to design and evaluate a matrix-type transdermal formulation containing nitrendipine with different ratios of hydrophilic (Hydroxy propyl methyl cellulose K-15) and hydrophobic polymer (eudragit RS 100) combinations plasticized with glycerine by the solvent evaporation technique. In the current study, effect of permeation enhancers include oleic acid, dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) is studied. FTIR studies were conducted to know the interference of the polymers in formulation and also physicochemical characteristics were studied for all prepared patches these include physical appearance, thickness, folding endurance, weight variation, percentage moisture loss, percentage moisture absorption, water vapour transmission, drug content and tensile strength. In vitro drug release studies were carried out with Franz diffusion cell using pH 7.4 phosphate buffer solution. Formulation patch F6 containing hydroxypropylmethylcellulose k15 (500mg) has given drug release of99.626at48hrs. Thus, Formulation F6 was optimized as a best formulation. Final formulation was subjected to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas models. All the evalutation studies were given satisfied results. Therefore, it was concluded that Transdermal patches were prepared were found to be satisfactory. And also it was found that developed nitrendipine transdermal patch has considerable action of control drug release in blood stream.

**Keywords:**Transdermal patches, Nitrendipine, Solvent evaporation technique.

## 1. INTRODUCTION

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Transdermal therapeutic system are defined as 'self-contained' discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation[1]. Transdermal drug delivery systems (TDDS) offer many advantages such as reduced side effects, elimination of first-pass metabolism and improved patient complience[2,3]. And also transdermal drug delivery shows various physicochemical properties, such as small molecular size, short half-life, low oral bioavailability and low dose, etc[4]. In recent times, transdermal patches are become most acceptable approach for patients. Several drugs were administered through transdermal route by matrix-type transdermal patches include aceclofenac, dexamethasone, terbutaline sulphate, atenolol, dilitiazem, etc. present-day, transdermal patches are applied in several therapeutical regions like smoking cessation, pain management, harmone replacement and treatment of heart disease[5-9].

Nitrendipine as calcium blocker shows peripheral vasodilation which effectively controls the blood pressure at small doses i.e. 5-20 mg per day[10]. It was orally well absorbed, but exhibits more fist-pass metabolism, which leads to poor bioavailability[11]. Very few studies were reported on transdermal patches using nitrendipine as an anti-hypertensive agent. The drug delivery into blood stream is based on types of penetration enhancers used in formulation of transdermal patches. Various studies were conducted on preparation of nitrendipine transdermal patches using azone[12] and d-limonene[13] as penetration enhancers. Gannu R et al. developed matrix type of nitrendipine transdermal patch by solvent evaporation technique[14]. They had also reported that prepared patches were evaluated through in vitro characterization using Franz Diffusion Cell system. Recently, several studies were performed using either HPC or PVP in combination with different eudragit polymers[15-17]. But the combination of HPMC K4 & K15 with eudragit RS 100 has not yet been reported. Hence, the current work is an attempt to formulate and evaluate the nitrendipine transdermal patches using the rare combination of HPMC K4 & K15 with eudragit RS 100 as excipients.

## 2. MATERIALS AND METHODS

### Materials

Nitrendipine was obtained from Mylan Laboratories Ltd,Hydroxypropylmethylcellulose was procured from Shreeji chemicals, Mumbai. Propylene glycol and Dimethyl formamide were taken from LobaChemie, Mumbai.Dibutyl phthalate, Potassium dihydrogen phosphate, Sodium hydroxide, Dimethyl sulfoxide, Glycerine, Carbopol 934 and Eudragit RS 100 were obtained from S.D. Fine Chem. Ltd., Mumbai. All the chemicals used were of laboratory grade.

### Equipments

Electronic single pan balance (DS-852J series, Essae - Teraoka Ltd), Digital pH- meter (Control Dynamics, Bangalore), Universal strength testing machine (Hounsfield, Horsham, U.K), Digital caliper (Aerospace), Magnetic hot plate (M B instruments, Delhi), Melting point apparatus (Techno scientific products), Digital ultrasonic cleaner (CD-4820 Techno scientific pdts), Locally fabricated aluminum mould(5*5), UV-Visible spectrophotometer (Shimadzu UV-1800pc, Japan), FT - IR spectrometer (IR affinity-1, Shimadzu, Japan).

### Formulation of transdermal patch

Transdermal patches of Nitrendipine were prepared by using polymers HPMC K-4 and K-15 by solvent evaporation technique for the formulations. A solution is prepared by dissolving weighed amount of drug and polymer separately in water. To the mixture Dibutyl phthalate, propylene glycol was added and mixed by using magnetic stirrer until a homogenous solution is

formed. The drug-polymer solution is casted in a bangle of area 16 $cm^2$ which is placed in a petridish. The mould was kept aside for 24hrs. Then, inverted funnel was placed over the mould to prevent the current of air. Finally, the patches were peeled from petridish, and preserved in desiccators for further studies.

**Table 1: formulation chart of nitrendipine transdermal patches ($F_1$-$F_{16}$)**

| Ingredients (mg) | Formulation code | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 | F16 |
| Nitrendipine | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| HPMC-$K_4$ | 100 | 200 | 300 | 400 | 500 | - | - | - | - | - | - | - | 100 | 200 | - | - |
| HPMC-$K_{15}$ | - | - | - | - | - | 500 | 200 | 300 | 400 | 100 | - | - | - | - | - | |
| Propylene glycol | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | - |
| Dibutylpthalate | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Water (mL) | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |

HPMC=Hydroxypropylmethylcellulose, q.s = quantity sufficient.

**Method of preparation of buffer solutions** [18]

**Phosphate buffer (pH 7.4) solution:** Fifty ml of 0.2M potassium dihydrogen phosphate was taken in 200 ml volumetric flask containing 39.1ml of 0.2M sodium hydroxide solution and the volume was made up to the mark with distilled water.

**Potassium dihydrogen phosphate (0.2M) solution:** Potassium dihydrogen phosphate (27.218g) was added to 1000ml volumetric flask containing distilled water and the volume was made up to the mark with distilled water.

**Sodium hydroxide (0.2M) solution:** Eight gram of sodium hydroxide was taken in 1000ml volumetric flask containing distilled water and volume was made up to the mark with distilled water.

**Analytical Method**

**Determination of λmax of Nitrendipine in phosphate buffer (pH 7.4) solution:** Preparation of Nitrendipine standard stock solution (1000µg/ml) in phosphate buffer (pH 7.4): standard stock solution of Nitrendipine was prepared by dissolving accurately weighed 100mg of Nitrendipine in the little quantity of phosphate buffer (pH 7.4) in 100 ml volumetric flask. Then, the volume was made up to 100 ml by using phosphate buffer (pH 7.4) to obtain the solution of 1000µg/ml, scanning of Nitrendipine by UV-spectrophotometer in phosphate buffer solution. From the standard stock solution, 1ml was diluted to 100ml with phosphate buffer solution. The resulting solution containing 10µg/ml was scanned between 200to400nm.

**Calibration curve of Nitrendipine in phosphate buffer solution (pH 7.4):** From the Nitrendipine standard stock solution (1000µg/ml), 10ml solution was diluted to 100ml using 7.4 pH phosphate buffer solution (100µg/ml).appropriate aliquots were take into different volumetric flasks and made up to 10ml with phosphate buffer solution, so as to get drug concentrations of 2.0 to 10.0µg/ml.The absorbencies of these drug solutions were estimated at λmax225nm. This procedure was performed in triplicate to validate the calibration curve.

**Evaluation of Transdermal Patches** [19-23]

**Melting point**[24]**:** A small amount of drug in a capillary tube was placed in a melting point apparatus and the temperature at which drug melts wasrecorded. It was performed thrice to get an average value of melting point.

**Determination of solubility**[25]**:** An excess amount of drug was taken and dissolved in a measured volume of distilled water in a glass vial to get a saturated solution. Then, the solution was sonicated and kept at roomtemperature for the attainment of equilibrium.

**pH Determination**[26]**:**The pH of nitrendipine was determined using potentiometer for freshly prepared 1% aqueous solution of nitrendipine.

**Physical appearance[27]:**Colour, surface texture and clarity of transdermal patches were physically examined.

**Drug –Excipient Compatibility study[28]:** FTIR spectra of the pure drug (nitrendipine) and polymer mixer was used to study the drug-polymer interactions in the formulation. A drug-polymer mixture was mixed with KBr (100:1) to prepare a sample pellet. Initially, the base line correction was taken using KBr powder. IRspectra of the mixture was taken at wave number range of 4000-400 $cm^{-1}$.

**Thickness uniformity[29]:**The patche thickness was measured using a Absolute Digimetic at three different places.

**Uniformity of weight[30]:**The patch of size 1x1 cm weight of the patch was cut and weight of each patch was taken individually and the average weight of the patch was calculated.

**Percentage moisture uptake:**The patches were weighed accurately and placed in a desiccator where humidity condition of 80-90% RH was maintained by using saturated solution of potassium chloride. After gaining the uniform weight, the patches were then taken out and weighed. Finally, the percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

**Water vapour transmission (WVT) rate:**In this study, transmission cells of equal diameter were used. These cells were washed thoroughly and dried in an oven. Accurately weighed 1 g of fused calcium chloride was taken in cells and the polymeric patches measuring 1 cm. then, the cells were kept in a closed desiccator containing saturated solution of potassium chloride to maintain 80-90% RH. The cells were taken out and weighed after 24 hrs. The rate of water vapour transmitted was calculated by the difference in weight.

**Folding endurance[31]:** The prepared films were measured manually by the folding endurance. A strip of film (2x2 cm) was taken and folded repeatedly at the same place till it was broken. Count the number of times the film was folded without breaking which gave the exact value of folding endurance.

**Tensile strength[31]:** The prepared patches **(**4 x 1 $cm^2$) were pulled by a pulley system, in which weights were slowly added to the pan till the patch was broken. The breakage of patch was due to excessive pulling force applied on the patch. The distance travelled by the pointer was noted. Finally, the tensile strength was caliculated by following formula.

Tensile strength = Tensile load at breat / Cross sectional area

**Drug content uniformity:**The patches were tested for the content uniformity. The patches of size 1 cm placed in a 100 ml volumetric flask containing pH 7.4 phosphate buffer. All suspended patches were stirred using a magnetic bead for 24 hrs to dissolve the patches. Further dilutions were made with phosphate buffer (pH 7.4). Finally, the observance of dilutions was measured at 209nm using UV-visible spectrophotometer.

**In-vitro release studies:** The fabricated patch were cut into 1$cm^2$ and placed on the semi permeable membrane (Egg membrane) and attached to the diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37±1$^0$c. The elution medium was stirred magnetically. The aliquots (1ml) was withdrawn at predetermined time intervals and replaced with same volume of pH 7.4 phosphate buffer. The drug content of sample was analysed using UV-spectrophotometer at 225nm.

**Drug Release kinetics [32]**

**Zero order release rate kinetics:** The obtained linear plot between cumulative percentdrugrelease (y-axis)

versus time (x-axis) indicates that the release rate data is fitted to the following equation

F = Kt

Where 'F' is the fraction of drug release, 'K' is the release rate constant and't' is the release time.

It obeys Zero-order release kinetics, with a slope equal to K.

**First order release rate kinetics:** The release rate date is fitted to the following equation

Log (100-F) = kt

If the plot (log % drug release Vs time) is linear that means it obeys first order release rate kinetics.

**Higuchi release model:**

The release rate data is fitted to the following equation

F = K.t ½

Where, 'K' is the release rate constant, 'F' is the amount of drug release, and 't' is the release time.

If the plot (cumulative drug released Vs square root of time) is straight line that indicates the drug release follows diffusion mechanism. And the slope is equals to 'K'.

**Korsmeyer- Peppas release model:** Mt / M∞ = K.tn

Where, 'K' isthe release constant,Mt / M∞ is the fraction of drug release, 't' is the release time and 'n' is the diffusional exponent for the drug release that dependent on the shape of the matrix dosage form.if the plot (Log of released Vs Log time)gives a straight line, indicating that the slope is equals to 'n' and the 'K' can be obtained from Y–intercept.

## 3. RESULTS

**Table 2: Calibration curve of Nitrendipine in pH7.4 phosphate buffer solution**

| Concentration | Absorbance at 225nm |
|---|---|
| 0 | 0 |
| 2 | 0.124 |
| 4 | 0.268 |
| 6 | 0.399 |
| 8 | 0.558 |
| 10 | 0.708 |

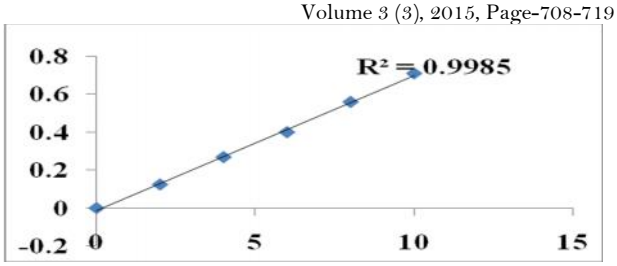


**Fig.1: Standard plot of Nitrendipine in phosphate buffer solution (pH 7.4) at 225nm**

**Table 3: Melting point, solubility, partition coefficient and pH of Nitrendipine**

| S.No | Parameters | Value of Parameters |
|---|---|---|
| 1 | MeltingPoint | 169±1.15°C |
| 2 | Solubility | 21.4mg/ml |
| 3 | Partitioncoefficient | 10.38 |
| 4 | pH | 3.46 |

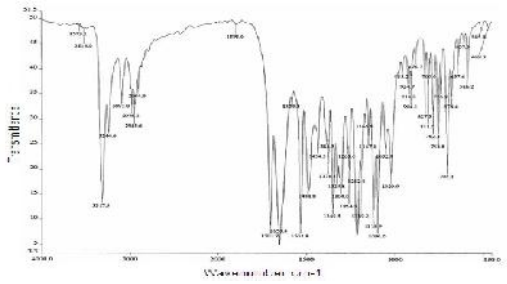

**Fig 2: IR spectrum of Nitrendipine pure**

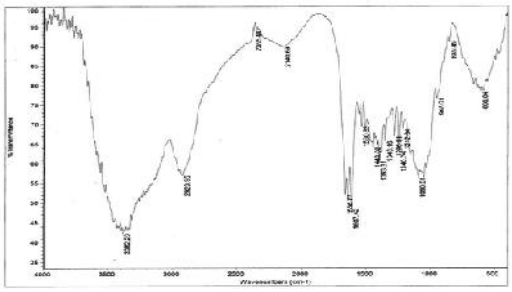

**Fig 3: IR Spectrum of Glycerin**

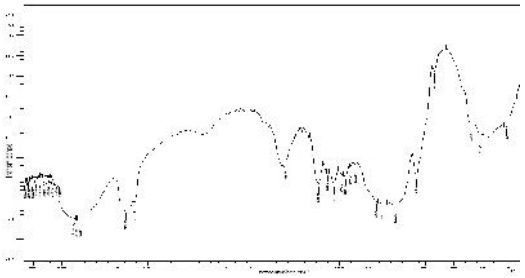

**Fig 4: IR spectrum of HPMC K-15pure**

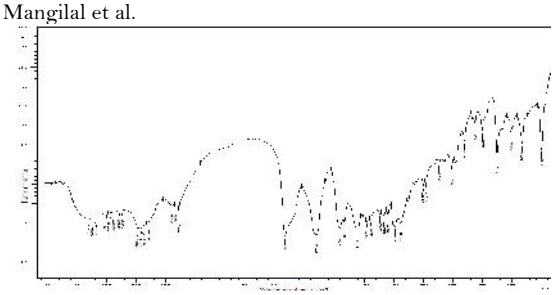

**Fig 5: IRspectrum of nitrendipine, HPMC K-15 and eudragit RS100 mixture**

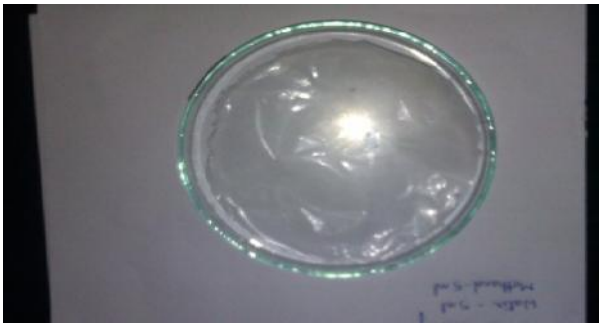

**Fig 6: Transdermal patch with HPMC_k15 polymer**

**Table4: Thickness uniformity data of F1 to F16 formulations**

| Formulation code | Trial1 mm | Trial2 mm | Trial3 mm | Mean±S.D.* mm |
|---|---|---|---|---|
| F1 | 0.22 | 0.2 | 0.21 | 0.21±0.001 |
| F2 | 0.19 | 0.195 | 0.194 | 0.19±0.0052 |
| F3 | 0.164 | 0.167 | 0.162 | 0.16±0.002 |
| F4 | 0.18 | 0.18 | 0.18 | 0.18±0.000 |
| F5 | 0.19 | 0.195 | 0.199 | 0.19±0.031 |
| F6 | 0.18 | 0.19 | 0.18 | 0.183±0.0057 |
| F7 | 0.19 | 0.195 | 0.194 | 0.190±0.0052 |
| F8 | 0.19 | 0.19 | 0.19 | 0.192±0.000 |
| F9 | 0.17 | 0.18 | 0.17 | 0.173±0.005 |
| F10 | 0.19 | 0.18 | 0.19 | 0.186±0.005 |
| F11 | 0.15 | 0.11 | 0.11 | 0.136±0.004 |
| F12 | 0.19 | 0.17 | 0.14 | 0.143±0.003 |
| F13 | 0.14 | 0.16 | 0.16 | 0.148±0.005 |
| F14 | 0.14 | 0.17 | 0.11 | 0.142±0.004 |
| F15 | 0.11 | 0.16 | 0.12 | 0.153±0.005 |
| F16 | 0.16 | 0.14 | 0.17 | 0.163±0.002 |

**S.D*:Standard deviation of three determinations**

**Table 5: Weight uniformity data of F1 to F16 formulations**

| Formulation code | Trial1 | Trial2 | Trial3 | Mean±S.D.* |
|---|---|---|---|---|
| F1 | 0.051 | 0.052 | 0.053 | 0.052±0.0012 |
| F2 | 0.030 | 0.032 | 0.031 | 0.032±0.004 |
| F3 | 0.041 | 0.042 | 0.043 | 0.041±0.021 |
| F4 | 0.034 | 0.034 | 0.032 | 0.033±0.016 |
| F5 | 0.035 | 0.032 | 0.034 | 0.046±0.0015 |
| F6 | 0.034 | 0.032 | 0.033 | 0.030±0.001 |
| $F_7$ | 0.053 | 0.052 | 0.054 | 0.054±0.0012 |
| F8 | 0.035 | 0.033 | 0.033 | 0.036±0.0016 |
| F9 | 0.023 | 0.020 | 0.021 | 0.0213±0.0015 |
| F10 | 0.042 | 0.044 | 0.042 | 0.0426±.0011 |
| F11 | 0.042 | 0.044 | 0.041 | 0.0442±.0017 |
| F12 | 0.041 | 0.041 | 0.043 | 0.0435±.0014 |
| F13 | 0.043 | 0.043 | 0.041 | 0.0412±.0016 |
| F14 | 0.045 | 0.044 | 0.046 | 0.0456±.0011 |
| F15 | 0.024 | 0.045 | 0.048 | 0.0436±.0014 |
| F16 | 0.012 | 0.041 | 0.041 | 0.0416±.0012 |

**S.D*:Standard deviation of three determinations**

**Table 6: Tensile strength data of F1 to F16 formulations**

| Formulation code | Trial1 | Trial2 | Trial3 | Tensilestrength (Kg±S.D.) |
|---|---|---|---|---|
| F1 | 2.215 | 2.212 | 2.216 | 2.20 ± 0.091 |
| F2 | 2.158 | 2.152 | 2.150 | 2.15 ± 0.077 |
| F3 | 1.589 | 1.587 | 1.582 | 1.58 ± 0.052 |
| F4 | 1.475 | 1.471 | 1.473 | 1.47±0.05 |
| F5 | 1.315 | 1.316 | 1.313 | 1.31 ± 0.311 |
| F6 | 0.834 | 0.837 | 0.832 | 0.83±0.047 |
| F7 | 0.562 | 0.561 | 0.564 | 0.56 ± 0.014 |
| F8 | 0.661 | 0.664 | 0.667 | 0.66 ± 0.208 |
| F9 | 0.318 | 0.317 | 0.314 | 0.31± 0.038 |
| F10 | 0.130 | 0.135 | 0.132 | 0.13 ± 0.021 |
| F11 | 0.122 | 0.142 | 0.142 | 0.11 ± 0.011 |
| F12 | 0.136 | 0.141 | 0.135 | 0.11 ± 0.031 |
| F13 | 0.146 | 0.136 | 0.112 | 0.12 ± 0.42 |
| F14 | 0.145 | 0.121 | 0.145 | 0.14 ± 0.124 |
| F15 | 0.110 | 0.112 | 0.175 | 0.11 ± 0.011 |
| F16 | 0.120 | 0.126 | 0.125 | 0.12 ± 0.001 |

**S.D*:Standard deviation of three determinations**

**Table 7: Folding endurance data of F1 to F16 formulations**

| Formulation code | Trial1 | Trial2 | Trial3 | Mean±S.D.* |
|---|---|---|---|---|
| F1 | 81 | 82 | 84 | 81±6.023 |
| F2 | 95 | 96 | 96 | 96±2.02 |
| F3 | 89 | 92 | 94 | 89±5.21 |
| F4 | 86 | 89 | 92 | 86±4.368 |
| F5 | 91 | 94 | 93 | 91±4.932 |
| F6 | 96 | 94 | 95 | 95±2.124 |
| $F_7$ | 90 | 92 | 88 | 88±6.254 |
| F8 | 87 | 85 | 86 | 84±4.124 |
| F9 | 95 | 94 | 96 | 94±3.210 |
| F10 | 91 | 94 | 102 | 95±6.027 |
| F11 | 94 | 91 | 99 | 96±6.154 |
| F12 | 96 | 93 | 100 | 91±6.027 |
| F13 | 92 | 91 | 96 | 93±6.244 |
| F14 | 94 | 98 | 95 | 94±6.214 |
| F15 | 91 | 93 | 98 | 96±6.204 |
| F16 | 92 | 92 | 101 | 95±4.077 |

**S.D*:Standard deviation of three determinations**

**Table 8: Percentage moisture uptake data of F1 to F16 formulations**

| Formulation code | Trial1 (%) | Trial2 (%) | Trial3 (%) | Mean±S.D* |
|---|---|---|---|---|
| | % | % | % | % |
| F1 | 1.28 | 1.27 | 1.28 | 1.29±0.21 |
| F2 | 1.57 | 1.54 | 1.55 | 1.58±0.363 |
| F3 | 1.64 | 1.62 | 1.64 | 1.64±0.542 |
| F4 | 1.72 | 1.68 | 1.70 | 1.68±0.124 |
| F5 | 1.74 | 1.72 | 1.70 | 1.72±0.952 |
| F6 | 1.61 | 1.66 | 1.62 | 1.66±4.124 |
| F7 | 1.69 | 1.74 | 1.72 | 1.71±0.247 |
| F8 | 1.83 | 1.82 | 1.84 | 1.83±0.12 |
| F9 | 1.90 | 1.91 | 1.92 | 1.92±0.134 |
| F10 | 1.95 | 1.94 | 1.94 | 1.96±0.17 |
| F11 | 1.90 | 1.91 | 1.92 | 1.92±0.134 |
| F12 | 1.42 | 1.42 | 1.89 | 1.93±0.169 |
| F13 | 1.84 | 1.53 | 1.91 | 1.91±0.158 |
| F14 | 1.77 | 1.87 | 1.92 | 1.89±0.175 |
| F15 | 1.87 | 1.75 | 1.88 | 1.88±0.145 |
| F16 | 1.91 | 1.91 | 1.86 | 1.92±0.112 |

S.D*: Standard deviation of three determinations 1.952

**Table 9: Water vapour transmission rate data of F1 to F16 formulations**

| Formulation code | Trial 1 | Trial 2 | Trial 3 | Mean ±S.D.* |
|---|---|---|---|---|
| F1 | 0.058 | 0.057 | 0.0079 | 0.0061±0.018 |
| F2 | 0.0072 | 0.0083 | 0.0063 | 0.0072±0.001 |
| F3 | 0.050 | 0.062 | 0.072 | 0.062±0.0012 |
| F4 | 0.0063 | 0.0075 | 0.0075 | 0.0071±0.0006 |
| F5 | 0.0063 | 0.0046 | 0.0072 | 0.006±0.001 |
| F6 | 0.0061 | 0.0062 | 0.0063 | 0.0062±0.001 |
| F7 | 0.066 | 0.0063 | 0.0066 | 0.0065±0.0002 |
| F8 | 0.007 | 0.0068 | 0.0081 | 0.0071±0.0012 |
| F9 | 0.0057 | 0.0075 | 0.008 | 0.007±0.0012 |
| F10 | 0.0049 | 0.0077 | 0.0083 | 0.0069±0.0018 |
| F11 | 0.0048 | 0.0071 | 0.0075 | 0.0068±0.0018 |
| F12 | 0.0047 | 0.0065 | 0.0071 | 0.0075±0.0018 |
| F13 | 0.0049 | 0.0077 | 0.0083 | 0.0069±0.0018 |
| F14 | 0.0048 | 0.0071 | 0.0075 | 0.0068±0.0018 |
| F15 | 0.0041 | 0.0074 | 0.0074 | 0.0078±0.0018 |
| F16 | 0.0044 | 0.0075 | 0.0074 | 0.0054±0.0018 |

S.D*: Standard deviation of three determinations

**Table 10: Percentage Drug content data of F1 to F16 formulations**

| Formulation Code | Trial1 % | Trial2 % | Trial3 % | % |
|---|---|---|---|---|
| F1 | 98 | 99.31 | 99.29 | 99.34 |
| F2 | 99.6 | 99.67 | 99.69 | 99.68 |
| F3 | 99.7 | 99.78 | 99.80 | 99.78 |
| F4 | 99.92 | 99.94 | 99.93 | 99.95 |
| F5 | 99.86 | 99.85 | 99.86 | 99.86 |
| F6 | 99.54 | 99.60 | 99.64 | 99.65 |
| F7 | 99.34 | 99.32 | 99.34 | 99.34 |
| F8 | 99.963 | 99.96 | 99.0 | 99.96 |
| F9 | 99.42 | 99.46 | 99.42 | 99.45 |
| F10 | 99.84 | 99.82 | 99.85 | 99.82 |
| F11 | 99.84 | 99.82 | 99.85 | 99.82 |
| F12 | 99.84 | 99.82 | 99.85 | 99.82 |
| F13 | 99.84 | 99.82 | 99.85 | 99.82 |
| F14 | 99.84 | 99.82 | 99.85 | 99.82 |
| F15 | 99.84 | 99.82 | 99.85 | 99.82 |
| F16 | 99.84 | 99.82 | 99.85 | 99.82 |

S.D*: Standard deviation of three determinations

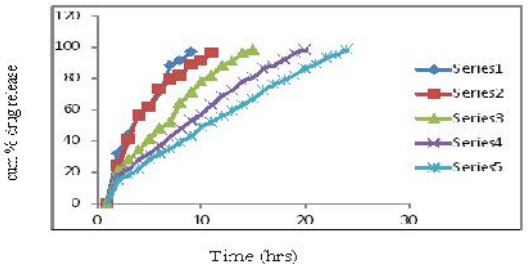


**Fig 7: Zero order release kinetic profile for F1-F5 formulation**

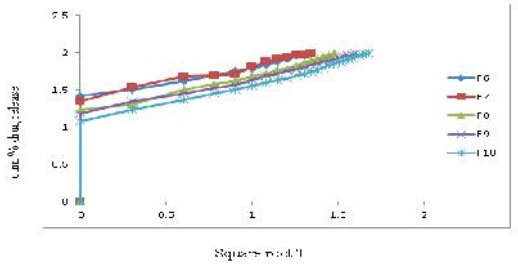

**Fig 8: Higuchi release kinetic profile of F6-F10 formulation**

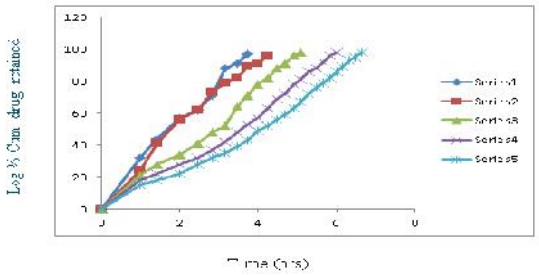

**Fig 9: First order release kinetic profile of F11-F16 formulation**

| Formulation | Zero order | First order | Higuchi matrix | Peppaskinetics | n'valuesfor Peppas |
|---|---|---|---|---|---|
| F1 | 0.9239±0.003 | 0.8742± | 0.829±0.002 | 0.9463±0.004 | 0.5799±0.026 |
| F2 | 0.9694±0.037 | 0.8749± 0.134 | 0.9427±0.001 | 0.9920±0.001 | 0.6184±0.034 |
| F3 | 0.8417±0.015 | 0.9427± 0.016 | 0.9896±0.005 | 0.8217±0.015 | 0.7872±0.030 |
| F4 | 0.9470±0.014 | 0.7253± 0.027 | 0.9325±0.015 | 0.9624±0.017 | 0.6215±0.021 |
| F5 | 0.9779±0.013 | 0.8432± 0.027 | 0.9959±0.002 | 0.9883±0.010 | 0.5679±0.006 |
| F6 | 0.9894±0.007 | 0.9830± | 0.8787±0.005 | 0.6184±0.035 | 0.5129±0.036 |

| | | | | | |
|---|---|---|---|---|---|
| | | 0.002 | | | |
| F7 | 0.9903±0.004 | 0.8573± 0.027 | 0.9896±0.005 | 0.9894±0.007 | 0.7872±0.030 |
| F8 | 0.8483±0.004 | 0.9870± 0.004 | 0.9767±0.001 | 0.9873±0.002 | 0.5855±0.003 |
| F9 | 0.8789±0.124 | 0.9657± 0.013 | 0.9830±0.002 | 0.9920±0.001 | 0.6105±0.029 |
| F10 | 0.8787±0.005 | 0.9864± 0.002 | 0.9840±0.008 | 0.9768±0.002 | 0.6184±0.0 |
| F11 | 0.8963±0.001 | 0.9721± 0.003 | 0.9821±0.001 | 0.9735±0.001 | 0.6184±0.012 |
| F12 | 0.8571±0.007 | 0.9864± 0.007 | 0.9840±0.006 | 0.9825±0.005 | 0.6184±0.023 |
| F13 | 0.9235±0.006 | 0.9239± 0.003 | 0.9840±0.003 | 0.9044±0.005 | 0.6184±0.021 |
| F14 | 0.8852±0.005 | 0.9864± 0.002 | 0.9840±0.007 | 0.9932±0.003 | 0.6184±0.058 |
| F15 | 0.9239±0.003 | 0.9864± 0.004 | 0.9840±0.002 | 0.9094±0.006 | 0.6814±0.035 |
| F16 | 0.8284±0.002 | 0.9756± 0.003 | 0.9392±0.004 | 0.9409±0.001 | 0.6481±0.053 |

**Table 12: model fitting of Formulation $F_6$**

| Formulation | Release kinetics |
|---|---|
| Zeroorder | 0.996±0.005 |
| Firstorder | 0.8135±0.004 |
| Higuchi matrix | 0.9901±0.002 |
| Peppaskinetics | 0.9851±0.001 |

## 4. DISCUSSION

Analytical Studies

The λmax of nitrendipine was found to be 209 nm which is same as that of literature review.

The regression coefficient ($r^2$) of nitrendipine drawn (fig.1) from calibration plot was 0.998. The absorbance values at different concentrations of nitrendipine were shown in table 2.

**Preformulation Studies**

Melting point of nitrendipine was found to be 150-160$^0$C. This value is same as that of the literature citation. Nitrendipine is soluble in phosphate buffer pH 7.4, methanol, chloroform, acetone and ether. But insoluble in distilled water. Partition coefficient determination study of nitrendipine was done with n-octanol and water. The logarithmic value of partition coefficient (log pKa) of nitrendipine was found to be 3.27, which indicates that nitrendipine is lipophilic in nature. The pH of freshly prepared 1% aqueous solution of nitrendipine was found to be 3.46. The physicochemical characteristics of nitrendipine were given in table 3.

Drug-excipient compatibility studies: As described in the methodology section, the FTIR studies were carried out for pure drug alone and along with polymers such as HPMC K-15, eudragit RS 100. It was observed that the identical peak of Nitrendipine (Fig.2) were not affected with other IR spectral peaks of polymer as shown in Figures 3, 4 & 5.This indicates there was no interaction between Nitrendipine and polymers.

**Evaluation of Patches**

Physical appearance: The patches were observed to be smooth and transparent in appearance (Fig.6)

Thickness: The average thickness of patches was noted with the help of Digital calipers. The thickness values of patches were given in table 4. These results indicate that there was no much difference in the thickness within the formulations. From the results, an increasing order of the thickness of patches was observed i.e. F6<F4<F3<F5< F2< F1<F4<F7<F8<F10< F12< F14<F3<F15<F16<F9

Weight uniformity: Drug loaded patches (1x1 $cm^2$) were tested for uniformity of weight and the results of weight uniformity were given in table 5. Lesser S.D. values indicate that the patches were uniform. From the results, an increasing order of the thickness of patches was observed. i.e. F5<F15<F3<F16<F2<F1<F4<F7<F8<F9< F12< F14<F3<F4<F5<F10

Tensile strength: Tensile strength was determined for drug-loaded patches by Hounse Field universal testing machine. The results of tensile strength were given in the table 6. The tensile strength of patches was depended on solubility of polymer added in the formulation. More the solubility of the polymer higher will be the tensile strength. In present study, the tensile strength of patches was increased with increased proportion of HPMC was added. It indicates that the soluble polymer develops cross linking better than insoluble polymer. An increasing order of the tensile strength of patches was observed i.e. F6 < F14<F12< F5 < F8 < F10<F12 <F3<F6<F5< F4 F1<F11<F7<F9<F2

Folding endurance: The recorded folding endurance of the patches was shown in table 7. It depicts that all formulations have good film properties. The order of the folding endurance of patches was observed i.e. F6 < F3<F4 < F6 < F9 <F1 <F8 <F12<F11< F2 < F13<F14<F7<F11<F10

Percentage moisture absorption: The recorded percentage moisture absorption of the patches was shown in table 8. These results shown that the moisture absorption of all the patches were within acceptable limit. An increasing order of the percentage moisture absorption of the prepared patches were in following order

F6<F3<F1<F5<F6<F4<F7<F9<F10<F8<
F13<F12<F11<F14<F16<F15

Water vapour transmission rate (WVTR): The water vapour transmission rate of different formulations was evaluated and the results were shown in table 9. The prepared nitrendipine patches from HPMC K-15 alone and in combination with eudragit RS 100 shown comparable WVTR of the prepared patches were in following order

F6<F8<F4<F5<F7<F2<F11<F15<F10< F2 < F9<F13<F12<F14<F10<F16

Drug content uniformity: Drug content of the patch was carried out to ascertain that the drug was uniformly distributed in formulation. The results obtained were shown in table 10. From the results (i.e. lowest S.D.values), it was clear that there was a proper distribution of nitrendipine in the film formulations. Therefore, it was concluded that the drug was uniformly distributed in all the formulation.

In-vitro release studies: In vitro release studies of nitrendipine patches were carried out in diffusion cell using commercial available semi permeable membrane and phosphate buffer (pH 7.4) as a diffusion medium. The release profile data of nitrendipine were given in table 11 respectively for patches $F_1$ to $F_{10}$. From these results, it was observed that 97.093 ± 1.71% of drug was released within 7hrs from $F_1$ and followed zero-order kinetics. The faster drug release rate is due to the use of hydrophilic polymer (HPMC K-15) alone. To sustain the drug release copolymer was added. Hence, eudragit RS 100 which is hydrophobic in nature was combined with HPMC K-15 to achieve sustain release of nitrendipine. The cumulative amount of drug released at 12 hrs from $F_2$ was found to be 97.37 ± 1.33 %. When compared to $F_1$ the drug release from $F_2$ was delayed from 7 hrs to 12 hrs. This effect was due to the use of copolymer, eudragit RS 100, which acted as the release-controlling polymer. The sustained drug release could be achieved by increasing the copolymer concentration in the formulation by keeping the total polymer concentration same i.e. 300 mg. In the formulations $F_3$ to $F_{10}$, weight of HPMC K-15 was decreased to 150 mg and eudragit RS 100 was increased to 150mg. It was found that only 85.53 ±2.403 % of nitrendipine was released from $F_3$ for 24 hrs. but it lacks complete drug release so it was necessary to conduct further study to release the complete drug from the prepared formulations.

Review of literature gave an idea of using permeation enhancer to improve the drug release from the formulation. In the current study, Oleic acid, DMF and DMSO were chosen as permeation enhancers used in formulations $F_4$, $F_5$ and $F_6$ respectively. Oleic acid was used in the formulation $F_4$ as a permeation enhancer and the drug release response from this patch was found to be 97.626 ± 1.142 %. The result reveals that oleic acid significantly increased the drug release when compared to the formulation without permeation enhancer i.e. $F_3$. DMSO and DMF were the most popularly used permeation enhancers in the research work reported for transdermal drug delivery. In the formulation $F_5$, DMSO was shown 96.37 ± 1.117 % of drug was released for 24 hrs. In the formulation $F_6$, DMF was used instead of DMSO as permeation enhancer and observed the response. It was clearly indicated that 94.573 ± 0.534 % of the nitrendipine was released for 24hrs. The patch containing oleic acid emerges as a better formulation. Because it shows maximum drug release by comparing all the patches which are sustained for 24 hrs.

The drug release kinetics was evaluated by making use of first order, zero order, korsemeyer-peppas equation and Higuchi's diffusion. Based on the higher regression values ($r^2$), the best fit model for $F_1$ and $F_2$ formulations was zero-order. Whereas, first order release for $F_3$, $F_4$, $F_5$, $F_7$, $F_8$, $F_9$, $F_{10}$, $F_{11}$, $F_{12}$, $F_{15}$ and $F_{16}$ Formulations. In addition, the release kinetics was following the diffusion controlled mechanism. The drug release kinetics of nitrendipine from all formulations ($F_1$-$F_{16}$) were shown in figure 7, 8 and 9. Release kinetic profile of nitrendipine TDDS for zero order, first order, peppas and Higuchi respectively. The peppas model is widely used when the release mechanismis not well known or when more than one type of release phenomenon could be involved. Formulation $F_6$ follows higuchi release and shows (Table 12) best drug release than other formulations.

## 5. CONCLUSION

The aim of the present study was to formulate transdermal patch of anti-hypertensive drug Nitrendipine using polymers HPMC K-4 and K-15, Propylene glycol (permeation enhancer) with Dibutylpthalate (plasticizer) by solvent evaporation method. From the preformulation studies such as solubility, melting point, pH, partition coefficient and absorbance maxima, it was confirmed that the drug was pure and not degraded. The compatibility between drug and polymer was studied by FTIR studies. The result shows that there was no significant interaction between drug and polymer was observed. Physicochemical parameters weight uniformity, thickness, tensile strength, folding endurance, percentage moisture uptake, percentage moisture loss, drug content and skin irritation study were carried out in order to know the pattern of release of nitrendipine from patches. In vitro release studies were formed with Franz diffusion cell using pH 7.4 phosphate buffer solution in a receptor compartment.

From the results of the drug content determination, it was assured that there was uniform distribution of drug in the patches and the deviations were within the acceptable limits. Among all the prepared formulations, $F_6$ containing HPMC K-15 (500mg) showed better drug release of 99.62 at 48hrs. the best formulation $F_6$ is being compared with anti-hypertensive drug clonidine (centrally acting alpha-agonist) catapress patch. The formulation $F_6$ showed better drug release than clonidine patch. On the basis of in-vitro characterization, it was concluded that Nitrendipine could be administered as transdermal patch.

The obtained best formulation of in-vitro studies are investigated in future for in-vivo studies. Further work

is to establish the therapeutic utility of this system by pharmacokinetics and pharmacodynamic studies on humanbeings.

## 6. REFERENCES


1. R.PnannerSelvam, Anoop Kumar Singh, T. Sivakumar, Transdermal drug delivery systems for antihypertensive drugs - A review, Int J Pharm Biomed Res 2010, 1(1), 1-8.
2. BhaskarK, Krishna Mohan C, Lingam M, Jagan Mohan S, Venkateswarlu V, MadhusudanRao Y, Bhaskar K, Anbu J, Ravichandran V., Development of SLN and NLC enriched hydrogels for transdermal delivery of nitrendipine: in vitro and in vivo characteristics, Drug DevInd Pharm. 2009, 35(1), 98-113.
3. Bhaskar K, Krishna Mohan C, Lingam M, Prabhakar Reddy V, Venkateswarlu V, MadhusudanRao Y, Development of nitrendipine controlled release formulations based on SLN and NLC for topical delivery: in vitro and ex vivo characterization, Drug DevInd Pharm. 2008, 34(7), 719-725.
4. Gannu, R., Vamshi, Y.V., Kishan V., Rao, Y.M.: (2007) Development of Nitrendipine transdermal Patches: In vitro and Ex vivo Characterization. Current Drug Delivery, 4, 69-76.
5. Patel et al. Formulation and evaluation of transdermal patch of Aceclofenac.International Journal of Drug Delivery.2009; 1: 41-51.
6. Rathore R P S, Chauhan C S, Naruka P S, Tanwar Y S, Chauhan LS. Transdermal Formulation of TerbutalineSulphate.Pharmacy online. 2006.
7. Mukherjee et al. Comparative studies between Povidone-Ethyl cellulose and Povidone-Eudragit Transdermal Dexamethasonematrix patches. Eur J Pharm Biopharm 2005;59: 475-83.
8. Aggarwal S S, MunjalPriya. Permeation Studies of Atenolol and Metoprolol Tartrate from Three Different Matrices forTransdermal Delivery. Indian J. Pharm. Sci. 2007; 69(4): 535-539.
9. Satturwar P M, Fulzele S V,Dorle A K. Evaluation of Polymerized Rosin for the Formulation and Development of Transdermal Drug Delivery System: A Technical Note. AAPS PharmSciTech.2005; 6 (4): E649-E654.
10. Karen, L.G.; Eugene, M.S. *Drugs* 1987, *33*, 123-155.
11. Kann J, Krol GJ, Raemsh KD, Burkholder DE, Levitt MJ.J. Cardiovasc. Pharmacol.1984; *6*: 968-973.
12. Ruan LP.; Liang, B.W.; Tao, J.Z.; Yim, C.H. J. Controll. Rel.1992, 20, 231-236.
13. Minghetti, P.; Cilurzo, F.; Montanari,L. Drug Dev. Ind. Pharm.1999, 25, 1-6.
14. Gannu, R., Vamshi, V.Y., Kishan, V., Madhusudan R.Y., Current DrugDelivery, 2007, 4, 69-76.
15. Aqil M, Ali A, Sultana Y, Najmi AK. Fabrication and evaluation of polymeric films for transdermal delivery of pinacidil.Pharmazie 2004; 59(8): 631-635.
16. ShindeAJ,GaralaKC,MoreHN.Developmentandcharacterizationoftransdermal therapeutics system of tramadol hydrochloride.AsianJPharm2008, 2, 265-269.
17. DasMK, BhattacharyaA, GhosalSK. Transdermal delivery of trazodon ehydrochloride from acrylic films prepared from aqueous latex.Indian J Pharm Sci 2006; 68(1):41-46.
18. A.Mittal, U. V.S. Sara, A. Asgar and M. Aqil, The effect of penetration enhancers on permeation kinetics of nitrendipine in two different skin models, Biol. Pharm. Bull. 31 (2008) 1766–1772; DOI: 10.1248/bpb.31.1766.

19. Aggarwal G. Development, Fabrication and Evaluation of Transdermal Drug Delivery-A Review. Pharmainfo.net. 2009
20. Kumar JA, Pullakandam N, Prabu SL, GopalV.Transdermal drug delivery system: an overview.Int. J. Pharm. Sci. Rev. and Res. 2010; 3(2): 49-54.
21. Barhate SD, Bavaskar KR, Saoji YS, PotdarM,Gholap TN. Development of Transdermal drugdelivery system of Ketoprofen. Int. J. Parma.Res. Develop. 2009; 1(10): 1-7.
22. Keleb E, Sharma RK, Mosa EB, AljahwiAZ.Transdermal Drug Delivery System-Design andEvaluation. Int. J. Adv. Pharm. Sci. 2010;1:201-211.
23. Kumar SR, Jain A, Nayak S. Development and Evaluation of Transdermal patches of Colchicine.Der Pharmacia Lettre. 2012, 4 (1):330-343.
24. Diez, H. Colom, J. Moreno, R. Obach, C. Peraire, J. Domenech, A comparative in vitro study of transdermal absorption of a series of calcium channel antagonists, J Pharm Sci. 1991, 80 (10), 931-934.
25. Shiva kumar VG, Mulla JS, Vinay BL. Formulation, characterization and evaluation of matrix-type transdermal patches of a model antihypertensive drug. Asian J Pharm 2009; 3: 59-64.
26. Meier P, Maillard M and Burnier.M. The future of angiotensin II inhibition in cardivascular medicine. Curr Drug Targets-Cardiovas & Haemat Dis 2005,5(1), 15-30.
27. Morgan TM, Reed BI, Finnin BC. Metered-Dose Transdermal Spray. In: Rathbone MJ, Hadgraft J, Roberts MS, editors. Modified-Release Drug Delivery Technology. New York: Marcel Dekker, Inc: 2002, p. 523-525.
28. K.Shivanand, S.A.Raju, B.Jayka.Mucoadhessive Bilayered Buccal Tablets of Tizanidine Hydrochloride. Int. J. Pharm. Tech. Res.2010; 2(3):1861-1869.
29. Patel RP, Patel G, Baria A. Formulation and evaluation of transdermal patch of aceclofenac. Int. J Drug Deliv 2009; 1: 41-51.
30. Ubaidulla U, Reddy MVS, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutica system of carvedilol: effect of hydrophilic and hydrophobic matrix on in vitro and in vivo characteristics. AAPSPharmSci Tech. 2007; 8(1): E13-E20.
31. Kusum Devi V. Saisivam S. (2003) Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev. Ind. pharm; 29: 495-503.
32. Ashu Mittal, Udaivirsinghsara, Asgarali.Formulation and evaluation of monolithic matrixpolymer films for transdermal delivery of nitrendipine. Acta.Pharm. 2009; 59: 383–393.

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