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STUDIES ON THE DEVELOPMENT OF TRANSDERMAL PATCHES OF NISOLDIPINE

A. ABDUL HASAN SATHALI[*] and L. MAGESHKUMAR

Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, MADURAI – 625020 (T.N.) INDIA

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ABSTRACT

The transdermal route of administration has been recognized as one of the highly potential routes. Transdermal drug delivery systems deliver the drugs across epidermis to achieve systemic effects and also it control, the delivery of drugs by employing an appropriate polymer. The objective of the present work was to develop a suitable transdermal drug delivery system of nisoldipine. Nisoldipine is a second generation dihydropyridine calcium antagonist and used in the treatment of stable angina and arterial hypertension. Polymeric films of nisoldipine were prepared by the solvent evaporation technique on mercury substrate. 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, PVP : EC, ERL 100 : EC, ERS100 : EC. They were evaluated for physicochemical parameter *in vitro* release and *ex vivo* permeation. Release of the drug from the films followed anomalous transport ($0.5 < n < 1$). Polymeric combination containing Eudragit RL 100 : EC in 2 : 3 ratio (ERL100 : EC; 2 : 3) (F 10) was considered as the best formulation with maximum drug release of 71.86% after 12 hrs. The flux of formulation F10 was found to be greater than the other formulations. The histopathological study confirmed that the formulations were free of potential skin toxicity.

Key words: Transdermal, Nisoldipine, Polymeric film, ERL100, Patches.

INTRODUCTION

The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of the drugs. Transdermal route has advantages over conventional modes of drug administration as it avoids hepatic first pass metabolism and improves patient compliance[1]. It excludes the variables that affect drug absorption from the gastrointestinal tract such as pH, enzymatic activity and drug food interactions. This approach of drug delivery is more pertinent in case of chronic disorders, such as hypertension, which require long term dosing to maintain therapeutic drug concentration[2]. Intensive research has shown that the transdermal route is a potential mode of delivery of lipophilic drugs in the systemic circulation[3]. Nisoldipine is a second-generation dihydropyridine calcium antagonist structurally related to nifedipine and used in the treatment of stable angina and arterial hypertension. It is also under investigation for the treatment of left ventricular dysfunction[4]. It was reported to be well absorbed following oral administration, but undergoes first pass metabolism; leading to poor bioavailability of 3.4-10%. In addition to pharmacokinetics properties, nisoldipine has low dose, low molecular weight (388.4), extensive first pass effect and lipophilic nature (octanol/water partition coefficient 3.63). All the above properties are enough indicators that nisoldipine might be a good choice as a drug candidate for transdermal delivery[5].

Available online at www.sadgurupublications.com
[*]Author for correspondence; E-mail: abdulhasan@hotmail.com; Mo.: +91-9443475400

The objective of the present work was to develop and characterize the nisoldipine Monolithic transdermal systems for *in vitro* release, *ex vivo* permeation, mechanical properties and histopathological studies.

EXPERIMENTAL

Materials and methods

Nisoldipine, Eudragit RL 100 (ERL100), Eudragit RS 100 (ERS100) was received as gift sample from Orchid Pharmaceuticals, Chennai. Hydroxyl Propyl Methyl Cellulose (HPMC), Ethyl cellulose, PVP K30 was also received as gift samples from Fourrts India Pharmaceuticals, Chennai. Dibutyl phthalate (DBP) (Loba chemie, India) and Dimethyl sulphoxide (DMSO) (BDH, England) were purchased locally. All other solvents and chemicals used were of analytical reagent grade.

Drug-polymer compatibility studies

The drug–polymer compatibility studies were carried out by using Infrared (IR) spectrophotometer (Shimadzu, Japan) and Differential scanning calorimetric (DSC) (DSC Q 200, Japan).

Infrared spectroscopic (IR) studies[6]

The infrared spectroscopic analysis was conducted to verify the possibility of interaction between drug and polymer. The IR spectrum of all samples (pure drug and physical mixture of drug & polymers) were obtained from an IR spectrophotometer (Shimadzu, Japan). The samples were scanned in the spectral region between 4000 cm^{-1} – 400 cm^{-1}.

Differential scanning calorimetric (DSC) studies[7]

The possibility of drug-polymer interaction was investigated by Differential scanning calorimetric (DSC Q 200, Japan).The DSC thermograms of pure drug and the polymers were recorded to study the interactions between drug and polymers. The sample was heated between 50^0 - 300^0C at a rate of 20^0C per minute.

Formulation of transdermal patches[3,8,2]

The transdermal patches were prepared by solvent casting technique employing a mercury substrate using different ratios of polymers. Polymer solutions were prepared using a mixture of dichloromethane and methanol as solvent. To the polymeric solution known weight of drug (Nisoldipine) was added and mixed slowly using magnetic stirrer for 20 minutes to get uniform dispersion. Dibutyl phthalate (plasticizer) and Dimethyl sulphoxide (permeation enhancer) was added at a concentration of 30% w/w of polymer. The solution was transferred to glass ring kept on the surface of mercury in petridish. Controlled solvent evaporation was achieved by placing an inverted funnel over the Petridish. These are left undisturbed at room temperature for one day. The patches could be retrieved intact by slowly lifting the rings from the mercury substrate. The films were stored between sheets of wax paper in desiccators.

Evaluation of transdermal patches

The prepared transdermal films were evaluated as follows:

Physical appearance[9]

All the transdermal patches were visually evaluated for their physical appearance colour, clarity, flexibility, and smoothness.

Weight variation[2]

Three patches from each batch were accurately weighed using a digital balance. The average weight and the standard deviation (SD) values were calculated from the individual weights.

Thickness of the patch[2]

The thickness of the transdermal patches was measured at three different places using a screw gauge and the mean values were calculated for each formulation.

Folding endurance[2]

The folding endurance of patches was determined by repeatedly folding the small strip of film at the same place till it was broken. The number of times the film could be folded at the same place without breaking is calculated as the folding endurance value.

Flatness[10]

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

Percentage moisture content[10]

The films were weighed individually and kept in a desiccators containing activated silica gel at room temperature for 24 hrs. The individual films were weighed repeatedly until a constant weight was achieved. The percentage of moisture content was calculated as the difference between initial and final weight with respect to the final weight.

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Estimation of drug content[11]

The transdermal patch of specified area (1 cm^2) was dissolved in sufficient amount of ethanol. The volume was made up to 10 mL. 0.1 mL was withdrawn from this solution and diluted to 10 mL. The absorbance of the solution was measured at 238.5 nm (using UV visible spectrophotometer. From the absorbance and dilution factor, the drug content in the film was calculated.

Tensile strength[12]

Tensile Strength of the film was determined by using the universal tensile strength testing machine (Universal Tensile Strength Tester. Ahmadabad). It consists of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (2 x 1 cm^2) was fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength was expressed as follows –

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross section area}}$$

***In vitro* drug release**[13]

A modified paddle over disc assembly (USP 23, Apparatus 5), was used for the assessment of the release of the drug from the patches. The transdermal patch was mounted on the disc and placed at the

bottom of the vessel. The dissolution medium was 900 mL of phosphate buffer pH 7.4. The apparatus was equilibrated to 32^{o}C ± 0.5^{o}C and operated at 50 rpm. The dissolution study was carried out for 12 hours. 5 ml of samples are withdrawn at regular intervals of 15 minutes for 1 hour and then 30 minutes for next 11 hour. The same volume of corresponding dissolution medium was replenished to maintain sink condition. The amount of nisoldipine released was determined by measuring the absorbance of the samples at 238.5 nm by UV-Visible spectrophotometer. Each test was performed in triplicate. The cumulative amounts of drug permeated per square centimetre of patches were plotted against time.

Study of drug release kinetic[14]

In order to investigate the drug release mechanism from patches, the percentage cumulative drug release data was analyzed with following mathematical expressions viz., zero order, first order and Higuchi model, Korsmeyer- Peppas model.

***Ex-vivo* permeation studies**[15]

A Franz diffusion cell with a diffusion area of 3.14 cm^2 was used for the permeation studies. Prior to this study, clearance was obtained from the Institutional ethical committee (Ref. No. 12677/E1/4/12). The skin was removed from the abdominal portion of an albino rat after sacrificing the animal. The hair and fat were removed after treating the skin with hot water for 45 sec. The abdominal skin was mounted between the cell halves so that the dermal side of the skin faced the receiver fluid. The stratum corneum side of the skin was kept in intimate contact with release surface of the transdermal patch. The receptor compartments was filled with 15 mL of Phosphate buffer pH 7.4 as diffusion media and stirred at 50 rpm on a magnetic stirrer, the temperature was maintained at 32^{o}C ± 0.5^{o}C. The amount of drug permeated was determined by withdrawing samples (1 mL) at regular intervals for a period of 12 hours and analyzed at 238.5 nm (shimadzu UV spectrophotometer).

Permeation data analysis[16]

The flux (µg/hr/cm^2) of nisoldipine was calculated from the slope of the plot of cumulative amount of nisoldipine permeated per cm^2 of rat abdominal skin at steady state against time using linear regression analysis.

Release kinetic of *ex vivo* permeability[14]

In order to investigate the drug release mechanism from patches, the percentage cumulative drug release data was analyzed with following mathematical model zero order, first order and Higuchi model, Korsmeyer's Peppas model.

Histopathology studies

Histopathological study is used to determine possible anatomical changes in rat skin. Abdominal skin of albino rats, a portion of skin (1 cm^2) was collected .The proximal dorsal skin was marked as A, and immediately stored in 10 % buffered formalin solution. The distal dorsal skin was marked as B and kept in phosphate buffer pH 7.4 at 32^{o}C for a 12 hour period after which it was stored in a 10 % buffered formalin solution. The skin portion was in contact with transdermal patch containing EC : EL100 with ratio of 3 : 2 is marked as D, and the skin portion that was in contact with pure drug solution was marked as C. Sample A was used as control for normal living skin. Sample B act as a control to represent the in vitro experiment without the presence of nisoldipine (In the form of pure drug or transdermal patch). The specimens were cut into section vertically. Each section was dehydrated using ethanol, embedded in paraffin for fixing and stained with haematoxylin and eosin. These samples were then observed under light microscope and

compared with control sample. Morphological changes in the skin (especially in epidermal layers) after the permeation experiments were observed visually and classified on a scale of A-D.

Class	Observation	Interfernce
A	Morphology of the sample looks exactly similar to the control	Nontoxic
B	Morphology looks almost similar to the control	slightly toxic
C	Morphology includes partial epidermal degradation With nuclei bleeding in to the dermal layers	Toxic
D	Morphology includes severe epidermal degradation with cell death	Severely Toxic

Scanning electron microscopy

The surface morphology of the transdermal patches before and after *ex vivo* skin permeation was analyzed by scanning electron microscopy.

RESULTS AND DISCUSSION

Drug-polymer interaction studies

Infrared Spectroscopic (IR) Studies

The IR Spectral analysis of pure nisoldipine showed characteristic peak at wave number 3320 cm^{-1} (N-H stretching), 3001 cm^{-1} (C-H stretching) and peak at 1701 cm^{-1} (Esterified carbonyl group) stretch. There was also a peak at 1555 cm^{-1} (Aryl nitro group) and at 1230 cm^{-1} (Ether absorption) and the same peaks at 3320, 3001, 1701, 1555, 1230 cm^{-1} were observed in the spectra of the medicated film. Hence, it may be concluded that there was no chemical interaction between the drug and the polymers[5]. The results of IR study were shown in Fig. 1.

Differential scanning calorimetric studies

In DSC thermograms, the endothermic melting transition of nisoldipine was observed at 150.15^{o}C (Melting point range of nisoldipine 150^{o}C -155^{o}C). The results of DSC study were shown in Figure 2. No shifts in the endothermic peak of nisoldipine or additional peaks were observed in the DSC thermograms of the physical mixture of nisoldipine and polymers (EC, HPMC, $PVPK_{30}$, ERS100 & ERL100) indicating that no chemical interaction had occurred between nisoldipine and polymer[6].

Formulation of nisoldipine transdermal patches

Formulation of transdermal patches of Nisoldipine using solvent evaporation technique

Transdermal patches of nisoldipine were successfully prepared using solvent evaporation technique. Matrix-type transdermal patches containing nisoldpine and variable combinations of HPMC/EC and PVP/EC, ERL100/EC and ERS100/EC were prepared as per the composition given in Table 1. In the present study total of 16 formulations were prepared using solvent evaporation technique. The common polymers such as EC, PVP, ERL, ERS, and HPMC are popular in controlled and sustained release matrix–type patches because of their compatibility with several drugs[16]. These polymeric combinations produced smooth patches when compared to patches prepared by a single polymer.

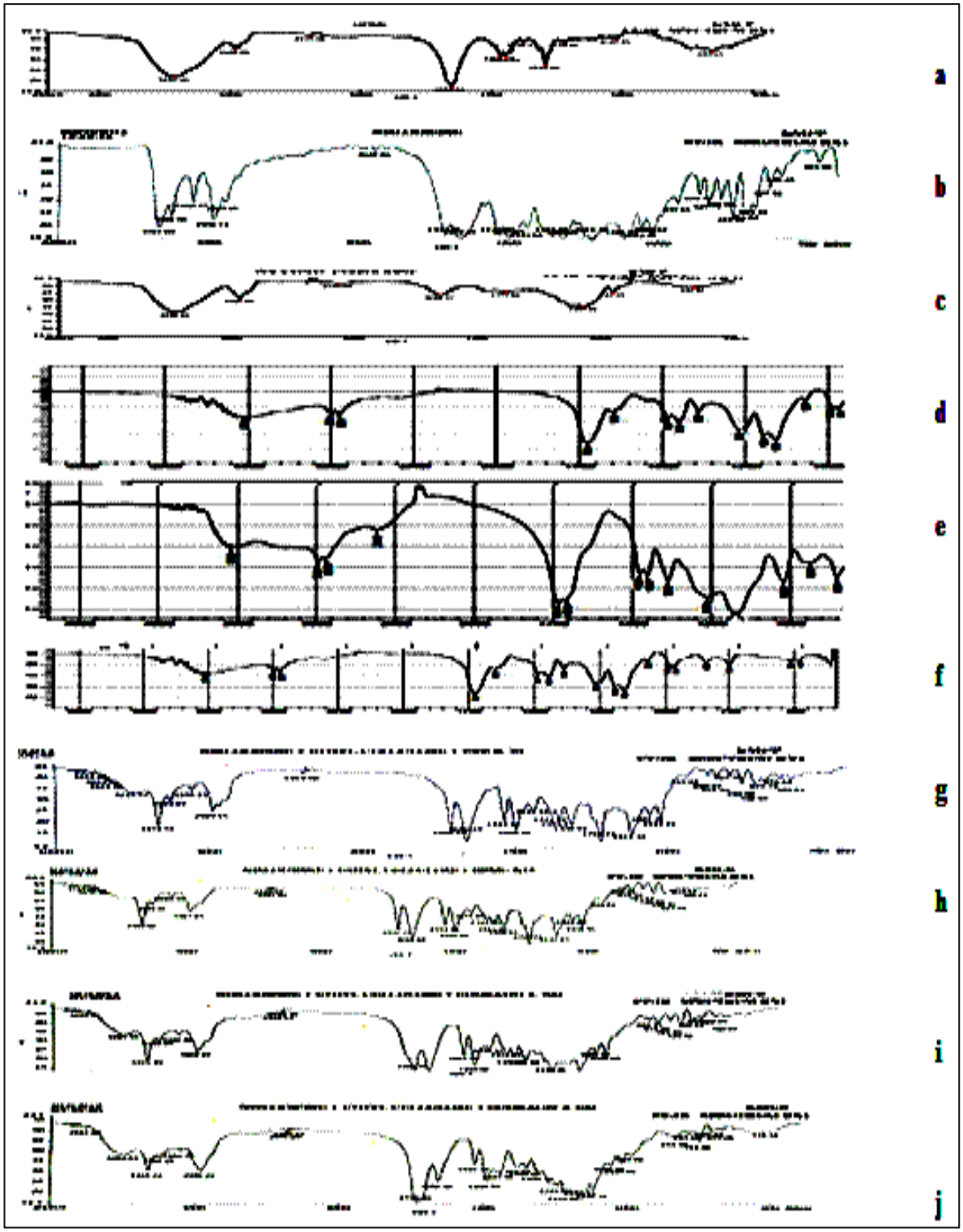

Fig. 1: FT-IR Spectra of Nisoldipine, 1 b: FT-IR Spectra of Hydroxy propyl Methyl Cellulose, 1 c: FT-IR Spectra of PVP, 1 d: FT-IR Spectra of Ethyl Cellulose, 1 e: FT-IR Spectra of Eudargit RL 100, 1 f: FT-IR Spectra of Eudargit RS 100, 1 g: FT-IR Spectra of Drug + Ethyl cellulose + PVP k_{30}, 1 h: FT-IR Spectra of Drug + Ethyl cellulose + HPMC k_{15}, 1 i: FT-IR Spectra of Drug + Ethyl cellulose + ERL100 100, 1 j: FT-IR Spectra of Drug+Ethyl cellulose + ERS 100

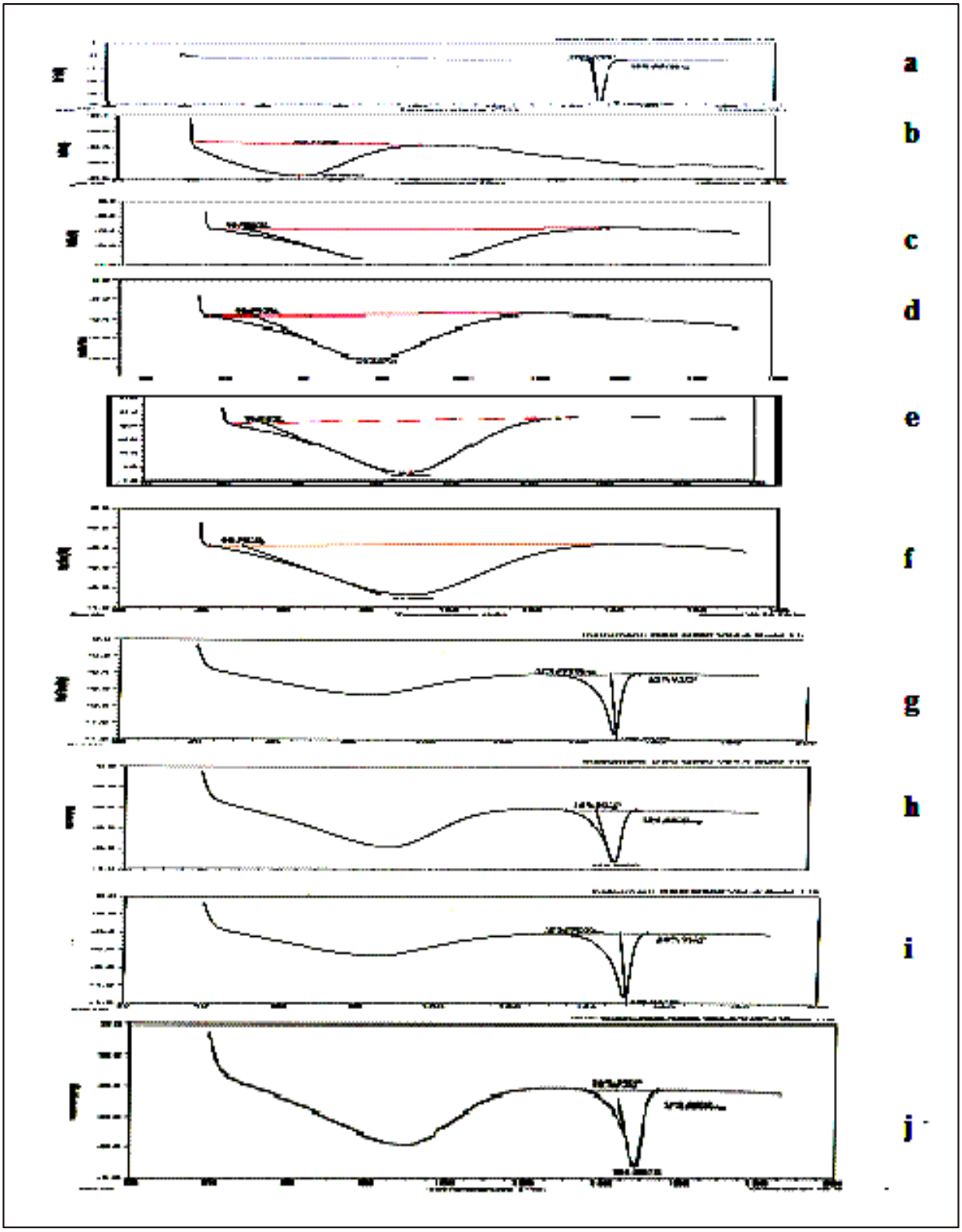

Fig. 2: DSC Thermogram Of Nisoldipine, 2b: DSC Thermogram Of Ethyl Cellulose, 2c: DSC Thermogram of Eudragit Rs 100, 2d: DSC Thermogram of Eudragit RL 100, 2 E: DSC Thermogram Of HPMC, 2 E: DSC Thermogram Of PVP K 30, 2g: DSC Thermogram of Drug + PVP K 30 + Ec, 2h: DSC Thermogram of Drug+ERL100, 2i: DSC Thermogram of Drug+ HPMC K15 +EC, 2j: DSC Thermogram of Drug+ HPMC K15 +EC

Table 1: Composition of transdermal patches of nisoldipine

S. No.	Formulation polymers code	Polymers	Ratio	Dibutylphalate (%W/W of polymers)	DMSO
1	F1	HPMC : EC	4 : 1	30%	30%
2	F2	HPMC : EC	3 : 2	30%	30%
3	F3	HPMC : EC	2 : 3	30%	30%
4	F4	HPMC : EC	1 : 4	30%	30%
5	F5	PVP : EC	4 : 1	30%	30%
6	F6	PVP : EC	3 : 2	30%	30%
7	F7	PVP : EC	2 : 3	30%	30%
8	F8	PVP : EC	1 : 4	30%	30%
9	F9	ERL100 : EC	4 : 1	30%	30%
10	F10	ERL100 : EC	3 : 2	30%	30%
11	F11	ERL100 : EC	2 : 3	30%	30 %
12	F13	ERL 100 : EC	1 : 4	30%	30%
13	F13	ERS 100 : EC	4 : 1	30%	30%
14	F14	ERS100 : EC	3 : 2	30%	30%
15	F15	ERS 100 : EC	2 : 3	30%	30%
16	F16	ERS 100 : EC	1 : 4	30%	30%

Evaluation of transdermal patches

Physical appearance

The method used for casting the film on a mercury substrate was found to be satisfactory. The patches containing the polymers HPMC and PVP was smooth, slightly sticky and flexible. The patches containing the polymer Eudragit (ERL100 & ERS 100) was flexible, smooth and transparent. The use of mercury substrate method helps to produce transparent, smooth and uniform patches[9].

Weight variation

The weight of the prepared patches (F1-F4) with different combination of polymers (HPMC: EC) ranged from 275.20 ± 0.55 mg to 302.72 ± 0.64 mg and 274.23 ± 0.72 mg to 301.24 ± 0.82 mg for (F5-F8) PVP/EC, 276.40 ± 0.42 mg to 302.73 ± 0.61 mg for (F9-F12) ERL100/EC and 252.50 ± 0.79 mg to 328.60 ± 0.75 for (F13-F16) ERS100/EC formulations. The results were shown in Table 2. 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[2].

Thickness of the patch

The thickness of the prepared patches (F1-F4) with different combination of polymers (HPMC : EC) varied from 0.160 mm to 171 mm respectively and PVP : EC ratio of polymeric films were ranged from 0.159 mm to 0.17 2 mm respectively. Formulation (F9-F12) prepared using different combination of polymers (ERL100 : EC) showed the thickness of the films ranged from 0.160 mm to 0.173 mm respectively and ERS 100 : EC ratio of polymeric films ranged from 0.158mm to 0.174 mm, respectively. The results indicated that the film thickness measurement ensured uniformity of the patches prepared by solvent evaporation technique. (Gupta J. R. D et al., 2011). The results were shown in the Table 2.

Table 2: Charactrization of transdermal patches

Formulation code	Weight ± sd (mm)	Thickness ± sd (mm)	Foldingendurance ± sd (No. of times)	% of moisture content ± sd (%)	% of drug content ± sd (%)
F1	275.20 ± 0.55	0.160 ± 0.007	47.66 ± 1.52	5.57 ± 0.36	94.6 ± 0.79
F2	284.94 ± 0.64	0.162 ± 0.003	38.33 ± 0.57	4.46 ± 0.30	91.18 ± 0.98
F3	292.86 ± 0.60	0.166 ± 0.001	25.00 ± 1.00	2.92 ± 0.17	90.47 ± 0.72
F4	302.72 ± 0.43	0.171 ± 0.005	12.66 ± 1.15	1.71 ± 0.29	88.94 ± 0.79
F5	274.23 ± 0.72	0.159 ± 0.003	53.33 ± 1.52	6.02 ± 0.24	95.85 ± 0.64
F6	276.26 ± 0.89	0.162 ± 0.003	48.33 ± 0.57	4.89 ± 0.15	93.17 ± 0.92
F7	291.14 ± 0.91	0.167 ± 0.001	32.00 ± 1.00	3.36 ± 0.33	89.91 ± 0.48
F8	301.24 ± 0.82	0.172 ± 0.006	16.66 ± 1.52	1.42 ± 0.36	88.93 ± 0.19
F9	276.40 ± 0.42	0.160 ± 0.001	103.3 ± 1.15	4.81 ± 0.23	95.59 ± 0.67
F10	288.66 ± 0.81	0.163 ± 0.004	98.66 ± 0.57	3.49 ± 0.37	94.38 ± 1.11
F11	299.18 ± 0.96	0.168 ± 0.006	93.66 ± 0.57	1.56 ± 0.30	90.30 ± 1.13
F12	302.73 ± 0.61	0.173 ± 0.002	64.00 ±1.00	1.11 ± 0.18	89.18 ± 0.42
F13	252.50 ± 0.79	0.158 ± 0.001	101.33 ± 0.57	4.76 ± 0.40	95.13 ± 0.52
F14	272.04 ± 0.72	0.164 ± 0.002	94.66 ± 1.52	3.46 ± 0.28	92.97 ± 0.64
F15	301.83 ± 0.58	0.167 ± 0.001	88.00 ± 1.00	1.82 ± 0.23	90.63 ± 0.55
F16	308.60 ± 0.75	0.174 ± 0.003	60.33 ± 1.15	0.96 ± 0.03	90.26 ± 1.02

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 12.66 ± 1.15 to 101.33 ± 0.57. The films were folded maximum of 101 times in the formulation F10 until the film cracks, which was taken as end point and minimum of 12 folds in the formulation F4. The results were shown in the Table 2. The results indicated that the patches had optimum strength ensuring their integrity and applicability. The folding endurance decreased with increasing concentration of ethyl cellulose polymers. The formulation (F_9-F_{16}) showed the highest folding endurance. The folding endurance of Eudragit patches was higher than patches containing HPMC, PVP polymers. The polymethacrylate polymers such as Eudragit RL100 and Eudragit RS100 were stable, possess good film making characters. The polymers have been used successfully in the design of various patches.

Flatness

The result of flatness study revealed that all the formulation had the difference in the strip lengths before and after longitudinal cut, indicating 100% flatness, and thus they could maintain a smooth surface when applied on to the skin.

Percentage moisture content

The results of moisture content studies were shown in Table 2. The results revealed that the moisture content was found to increase with increasing the concentration of hydrophilic polymers in all the formulations. The moisture content of the polymers was found to be in the following order PVP > HPMC > ERL100 > ERS 100. 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[16]. The low moisture absorption protects the material from microbial contamination and bulkiness of the patches.

Estimation of drug contents

The drug contents of all the patches (F1-F16) were in the range of 95.85% ± 0.64% to 88.93 ± 0.19%. The results of drug contents range were shown in Table 2.These results indicated that there was a fare distribution of drug in the formulations.

Tensile strength

The Tensile strength test enables to study the mechanical properties of the patches. These properties are important to exhibit desirable resistance to external forces, so that damage, such as tearing will not occur during storage or use. The results of tensile strength range were shown in Table 3.

Table 3: **characterization of tensile strength of nisoldipine transdermal patches**

Formulation code	Tensile strength (Kg/cm^2)
F_1*	NIL
F_2*	NIL
F_3	3.32
F_4	2.14
F_5*	NIL
F_6	3.74
F_7	3.24
F_8	2.40
F_9	4.42
F_{10}	4.01
F_{11}	3.13
F_{12}	2.96
F_{13}	4.29
F_{14}	3.92
F_{15}	3.24
F_{16}	NIL

* The formulations of F1, F2 and F5 could not withstand the mechanical properties

The mean value was found to vary between 4.42- 2.14 Kg/cm^2 .The tensile strength of patches was found to be in the following order F9 > F13 > F10 > F14 > F6 > F3 > F7, F15 >F11 > F12 > F8 > F4. These results indicated that increasing the concentration of hydrophilic polymer increased the tensile strength. The polymethacrylate polymers such as Eudragit RL100 and Eudragit RS100 were stable and possessed good film making characters. The polymers have been used successfully in the design of various patches. The formulations of F1, F2 and F5 could not withstand the mechanical properties due to poor film forming properties of polymer at that particular composition.

In vitro drug release studies

The results of *in vitro* drug release studies of the nisoldipine transdermal patches were shown in Figures 3a-3d. Formulation (F1-F4) prepared using different combination of polymers (HPMC : EC) (4 : 1, 3 : 2, 2 : 3, 1 : 4) showed the cumulative percentage drug release of 86.97%, 75.3%, 70.07%, and 66.44% at the end of 12 hours. Formulation (F4-F8) prepared using different combination of polymers (PVP : EC) (4 : 1, 3 : 2, 2 : 3, 1 : 4) showed the cumulative percentage drug release of 88.24%, 83.26%, 78.98%, and 72.45% at the end of 12 hours. Formulation (F9-F12) prepared using different combination of polymers (ERL 100 : EC) (4 : 1, 3 : 2, 2 : 3, 1 : 4) showed the cumulative percentage drug release of 79.79%, 71.86%, 68.76% and 63.74% at the end of 12 hours. Formulation (F13-F16) prepared using different combination of polymers (ERS 100: EC) (4 : 1, 3 : 2, 2 : 3, 1 : 4) showed the cumulative percentage drug release of 78.38%, 70.84%, 66.91%, and 64.04% at the end of 12 hours.

The drug release was found to increase on increasing the concentration of hydrophilic polymers in the polymer matrix. This is due to the fact that dissolution of an aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores.

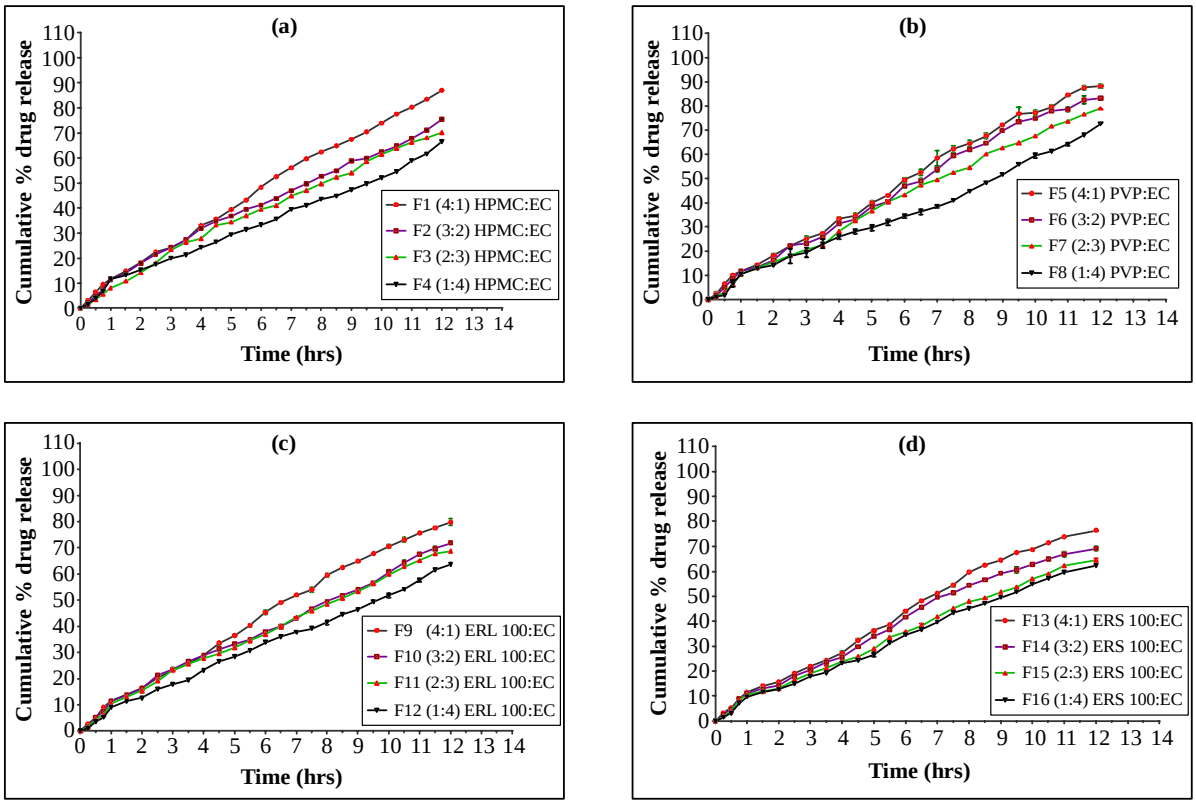

Fig. 3: Comparison of *in vitro* release profile of nisoldipine transdermal patches containing different polymers at different ratios

The formation of such pores leads to decrease in the mean diffusion path length of drug molecules to release in to the diffusion medium and hence cause a higher release rate[9]. The results indicated that the hydrophobic nature of polymer which has less affinity for water results in decrease in thermodynamic activity of the drug in the film and decreased drug release. From the above studies it was concluded that the release pattern was controlled by combination of hydrophilic and hydrophobic polymers. Partitioning

between hydrophobic polymers and diffusion medium was very less indicating that the membrane retarded the release of drug from the reservoir.

Study of drug release kinetics

The description of dissolution profile by a model function has been attempted using different kinetics (zero order, first order, Higuchi square root model, Korsmeyer's Peppas model[7].All the formulations (F1-F16) followed zero order release kinetics. The correlation coefficients (R2) were found to be in the range of 0.989-0.996. Further to find out whether diffusion was involved in the drug release, the data was subjected to Higuchi. The line obtained were comparatively linear (r^2 = 0.954-0.985) suggesting that the diffusion might be of drug release. To confirm further release mechanism of drug, the data was subjected to Korsmeyer's Peppas equation. The release exponent 'n' value (0.5 < n < 1) of korsmeyer's peppas model indicated that release of drug from all the patches followed anomalous transport[2].

***Ex-Vivo* permeation studies**

The formulation F10 (ERL100 : EC) (3 : 2), F14 (ERS100 : EC) (3 : 2) was selected for ex vivo permeability study on the basis of % moisture content (F10 = 3.49 ± 0.37, F14 = 3.46 ± 0.28) and mechanical properties like tensile strength (F10 = 4.01 Kg/cm^2., F14 = 3.92 Kg/cm^2) and *in vitro* release kinetics. The results of *ex vivo* drug permeation study were shown in Fig. 4.

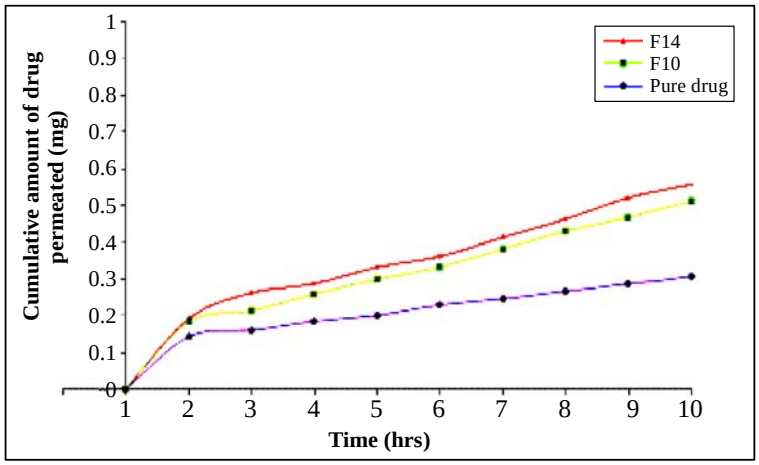

Fig. 4: Comparison of *ex vivo* permeability release studies of F10, F14 & pure drug

The cumulative amount of drug permeated from the formulation F10 (ERL100 : EC) (3 : 2) was found to be 0.698 mg at the end of 12 hours where as it was found to be 0.658 mg for F14 (ERS100 : EC) (3 : 2) and 0.421 mg for pure drug solution. From the above studies it was concluded that the use of Eudragit RL100 and Eudragit RS100 polymeric dosage forms controlled release of drugs. ERL is freely permeable to water, where as ERS is slightly permeable[16]. The result of permeation from the transdermal patches of nisoldipine through the rat abdominal skin confirmed that nisoldipine was released from the formulation and permeated through the skin and hence could possibly permeate through human skin[8].

Permeation data analysis

The flux achieved during *ex vivo* permeation study was found to be 55.13 µg/cm^2/hr for F10 and 48.78 µg/cm^2/hr for F14. From the above studies it was concluded that use of Eudragit RL100 and Eudragit RS100 polymeric dosage forms controlled release of drugs, where ERL100 was freely permeable to water and ERS100 was only slightly permeable to water[16].

Release kinetics of *Ex vivo* permeability

The description of dissolution profile by a model function has been attempted using different kinetics (zero order, first order, Higuchi square root model, Korsmeyer's Pappas model[8]). Formulation F_{10} and F_{14} showed zero order release kinetics. The correlation coefficient values (r^2) were found to be 0.963 and 0.971. The formulations F_{10} and F_{14} were followed Higuchi mechanism. The correlation coefficient (r^2) values were found to be 0.968 and 0.962. The n values of korsmeyer's peppas model indicated that the release of drug from the formulation F_{10} (n=0.570) and the formulation F_{14} (n = 0.526) followed Non-fickian diffusion mechanism. The result of drug permeation from transdermal patches indicated that drug release by Non-fickian mechanism was predominated ($0.5 < n < 1.00$) defining a drug transport with a combination of drug diffusion and polymer relaxation process.

Histopathology studies

The results of histopathological studies were shown in Table 3 and Fig. 4a-4d. The sample as A (normal healthy rat abdominal skin) showed intact stratum corneum with muscle bundle and fat. The result indicated that there were no histological abnormalities found in the skin section of the control group. The sample as B (Rat abdominal skin in contact with phosphate buffer pH 7.4) showed fibro fatty tissue, inflammatory cell infiltrate and oedema. Identical changes were presented in the samples from group C (Rat abdominal skin in contact with nisoldipine pure drug solution for 12 hrs), group D (Rat abdominal skin in contact with F10 Formulation containing ERL100 : EC. The result indicated that there was no anatomical degradation in the morphology of the skin sample exposed to formulation (F10) and pure drug solution.

Sample code	Observations
A (untreated skin)	Skin with inter muscular oedema, inflammatory cell infiltrate
B (Skin treated with Phosphate buffer pH7.4)	Skin with fatty tissue and sparse inflammatory cell infiltrate
C (Skin treated with nisoldipine pure drug)	Skin thinned out epidermis with autolytic changes
D (Skin treated with Formulation F10)	Skin thinned out epidermis with matrix oedema and the stoma

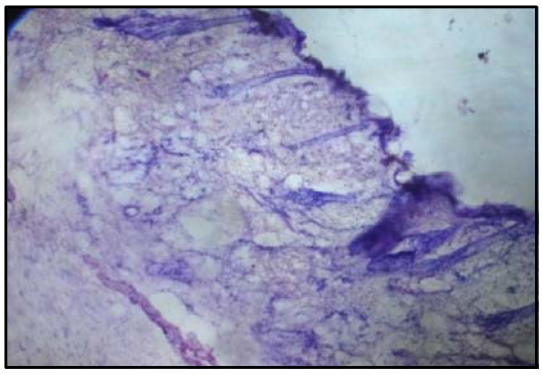

Fig. 4a: Untreated skin

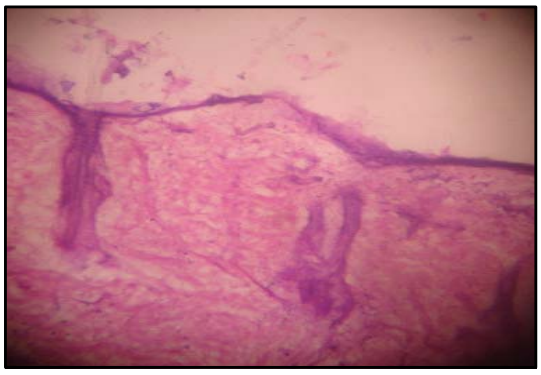

Fig. 4b: Skin treated with phosphate buffer pH 7.4

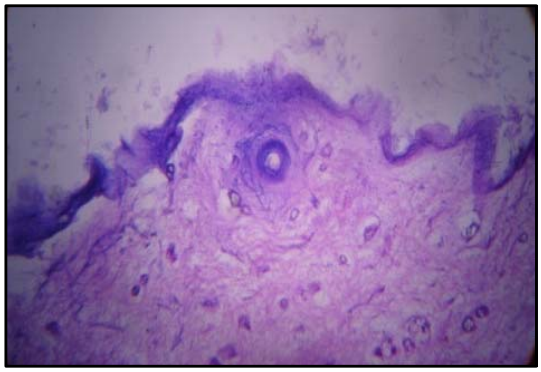

Fig. 4c: Skin treated with formulation f 10

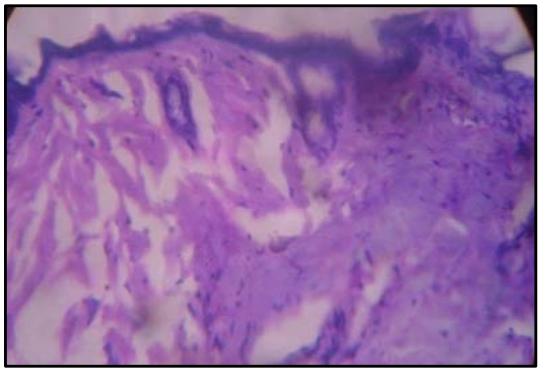

Fig. 4d: Skin treated with Nisoldipine pure drug solution

Scanning electron microscopy

The surface morphology of the transdermal patches before and after *ex vivo* permeation study was scanned using a scanning electron microscope. The results were shown in Fig. 5a-5 b.

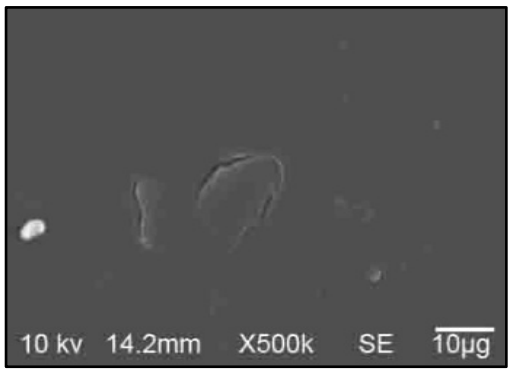

Fig. 5a: Before permeation studies

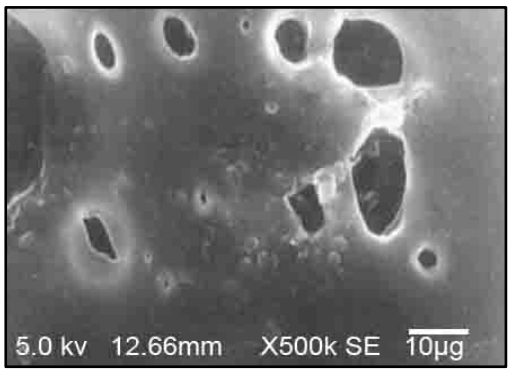

Fig. 5b: After permeation studies

Fig. 5a, showed morphology of the batch before *ex vivo* permeation study which indicated that the uniform distribution of drug in the polymer matrix.

Fig. 5b, displayed the behaviour of the polymer-matrix after the release of drug molecules. From the above result it was observed that the formulation maintained the elastic nature of the film after the release of drug molecules without affecting the other parts of the patch.

CONCLUSION

Based on the results of this study, it can be concluded that a well-controlled release and effective skin permeation of the drug was achieved by the formulation containing (F10) (ERL 100 : EC) (2 : 3). The physicochemical evaluation indicated the stability of the developed transdermal patches. The *ex vivo* studies has proved the feasibility of controlled transdermal delivery of nisoldipine in adequate quantity in to the systemic circulation. The controlled release of drug from the transdermal patches suggested that the frequency of administration can be reduced. The transdermal patches can improve the bioavailability of the nisoldipine by avoiding hepatic first pass metabolism. Further work is to establish the therapeutic utility of this system by pharmacokinetics and pharmacodynamic studies on human beings.

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