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Development and Characterization of Nisoldipine Matrix Type Transdermal Films; In vitro and Ex-vivo Evaluation

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Abstract

The purpose of this study was to fabricate the transdermal films of a low oral bioavailability drug Nisoldipine (5%) employing a combination of hydrophilic and hydrophobic polymer. The films were developed by solvent evaporation technique. The polymeric matrix contains Ethyl cellulose/Eudragit RS 100 and HPMC E-15. The effect of hydrophilic and hydrophobic polymers on the physicochemical and mechanical properties, such as weight variation, thickness, moisture uptake, moisture content, and tensile strength, elongation at break was evaluated. *In-vitro* release and *ex-vivo* permeation across the rat skin was studied using the Franz diffusion cells. The tensile strength of the NS6 and NSE5 were found to be 0.9±0.21 and 1.9±0.10 kg/mm^2.The films developed in the ratio of 15:5 (NS6) and 12.5:7.5 (NSE5) using HPMC E15-ERS 100 and HPMCE15- EC showed maximum drug release and *ex-vivo* permeation (NS6: 953 µg and NSE5:895 µg).The flux of NS6 and NSE5 was 13.03 µg/cm^2/hr and 11.77 µg/cm^2/hr. The data of release kinetics using different kinetic models indicated that release from optimized formulations followed zero order release kinetics with non fickian diffusion pattern. FTIR studies revels that there was no interaction between the drug and polymer and were found to be compatible. Matrix type transdermal films can be fabricated employing hydrophilic and hydrophobic polymers with suitable mechanical properties.

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Keywords: Nisoldipine; Matrix films; Mechanical properties; *In vitro* drug release; *Ex –vivo* skin permeation; Release kinetics.

1. Introduction

The transdermal route of administration is considered as one of the potential route for the local and systemic delivery of drugs [1-2]. Drug delivery through skin has a number of significant advantages over many other routes of drug administration, such as painless and simple application, ability to avoid problems of gastric irritation, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, pH and emptying rate effects, reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy, rapid termination of therapy by removal of the device or formulation, provide a sustained release of drug at the site of application; the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with injections [3-4] .

Nisoldipine is a calcium antagonist of the 1, 4-dihydropyridene class, can reduce vascular resistance and blood pressure by inhibiting calcium uptake of myocardial and smooth muscle cells [5].Immediate-release (5 and 10 mg) and controlled-release (10, 20, 30 mg and 40 mg) oral preparations for NSP are available in the market for the treatment of hypertension and angina pectoris [6-8]. Following oral administration, Nisoldipine is rapidly absorbed from the gastrointestinal tract, but the oral bioavailability remains low (5%) because of significant first-pass hepatic metabolism [9]. Nisoldipine also has a short plasma half-life of 7-12 hrs. Long term therapy of hypertension by Nisoldipine oral administration may result in poor patient compliance because of low bioavailability and short plasma half-life, leading to increase frequency of administration, therefore an alternative route of administration is needed. The aims of the present study was to develop matrix type transdermal films of NSP employing various ratios of hydrophilic and hydrophobic polymer combinations, evaluate the physicochemical characterization and mechanical properties and conduct the *in vitro* release and *ex-vivo* permeation studies through rat abdominal skin. The purpose was to provide the delivery of the drug at a controlled rate across intact skin to improve the drug concentrations in layers of skin.

2. Materials and Methods

2.1 Materials

Nisoldipine was obtained as gift sample from Orchid Chemicals and Pharmaceuticals, Chennai, Tamilnadu, India. Eudragit RS100, Ethyl cellulose, HPMC E-15 were obtained as gift samples from Dr. Reddy's Laboratories, Hyderabad, India. All other chemicals and solvents used were of analytical reagent grade.

2.2. Methods

2.2.1. Preparation of transdermal Films

Nisoldipine matrix type transdermal films were prepared by film casting technique using different ratios of Eudragit RS 100 or Ethyl cellulose and HPMC E-15. Weighed quantity of polymers was dissolved in 20mL of

solvent mixture consisting of 1:1 ratio of dichloromethane and Methanol. The polymeric solution was vortexed and kept for swelling for 8 hrs. Weighed quantity of Nisoldipine was dissolved in 5 mL of solvent mixture. The drug solution and propylene glycol (15% W/V) as plasticizer was added to the polymeric solution and was vortexed for 5 minutes. The mixture was kept aside for 10 minutes to remove the entrapped air bubbles and was transferred into petri plates. The rate of evaporation of the solvent was controlled by inverting cut funnel over the petri plate. Drying of these films was carried out at room temperature for overnight and then in vacuum oven at room temperature for 10 hrs. The films were carefully removed, cut to the size each having 1.78 cm X 1.78 cm (3.56cm^2) and stored in desiccators.

2.2.2. Weight and thickness variation assessment

Each fabricated film was prepared in triplicate and ten circular films having an area 1.78 cm X 1.78 cm (3.56 cm^2) were cut from each plate. The weight was measured using digital balance. The thickness of film was measured at different sites using digital screw gauge.

2.2.3. Estimation of drug content

The fabricated polymeric films were assayed for drug content. Three films from each formulation series were taken, cut into small pieces and was dissolved in 10 mL of solvent mixture (1:1 ratio of DCM: methanol). The resulting mixture was diluted up to 100 mL with pH 7.4methanolicphosphate buffer (40:60). The solution was filtered through membrane filter (0.45 µ) and the drug content was measured using UV spectrophotometer.

2.2.4. In vitro drug release studies

Drug release from the transdermal patch was studied using vertical Franz diffusion cells with a receptor compartment capacity of 17mL. The patch of 3.56cm^2 was mounted on the dialysis membrane placed in between the donor and receptor compartment of the diffusion cell. The receptor compartment was filled with methanolic phosphate buffer pH 7.4 (40:60). The whole assembly was place on the magnetic stirrer and solution in the receptor compartment was stirred continuously using magnetic beads at 350rpm, the temperature was maintained at 37 ±0.5 °C. An aliquot of 2mL were withdrawn at pre-determined time intervals and analyzed for the drug content spectrophotometrically. The receptor phase was replenished with an equal volume of methanolicphosphate buffer pH 7.4 (40:60) at each sample withdrawal to maintain the in vitro sink conditions [10].

2.2.5. In –vitro release Kinetics

Different kinetic models, zero order, first order [11], Highuchi and Kosrsmeyer expressions [11-12]were applied to interpret the drug release kinetics to know the mechanism of drug release from these matrix systems with the help of equation's (1- 4).

$$M_t = M_o + K_o\, t \text{ ----------(1)}$$

$$LnM_t = LnM_o + K_1 t \text{ ----------(2)}$$

$$M_t = K_H t^{1/2} \text{----------(3)}$$

$$M_t/M_\infty = K_k t^n \text{ ----------(4)}$$

M_t cumulative amount of drug release at time t; M_o, is the initial amount of drug K_o, K_1, K_H and K_k are rate constants for zero order, first order, Highchi and Korsemeyer model respectively; M_t/M_∞ is the fraction of drug release at time t n, release exponent indicative of the operating release mechanism. The correlation coefficient values (r^2) presented in table 3.

2.2.6. Percentage moisture uptake

Circular films having an area 1.78 cm X 1.78cm (3.56 cm^2) were weighed accurately and placed in desiccators containing 100 mL of standard of aluminium chloride solution in order to maintain 79.5 % RH. After 72 hrs, the films were taken out and weighed. The percentage of moisture uptake was calculated as difference between the final and initial weight with respect to the initial weight [13].

2.2.7. Percentage moisture content

The prepared films were weighed accurately and kept in a vacuum desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patch was individually weighed until they showed a constant weight. The percentage of moisture content was calculated as a difference between initial weight and final weight with respect to final weight [14].

2.2.8. Mechanical Properties

Mechanical properties of the fabricated films were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, and UK), equipped with 25 kg load cell. The Tensile strength (T.S) and elongation of break (E.B) were measured using the film strip (60 × 10mm) free from air bubbles or any physical imperfections. The film strip (60 × 10mm) was held between two clamps positioned at a distance of 3 cm. During measurement, the top clamp at a rate of 2 mm s^{-1}pulled the strips to a distance till the film broke. The force and elongation were measured when the films were broken. The mechanical properties were calculated using the equation 5 and 6.

$$\text{T.S (Kg mm}^{-2}\text{)} = [\text{Force at break (Kg)/ Initial cross sectional area of the patch (mm}^{-2}\text{)}] \text{ ..... (5).}$$

$$\text{E.B (\%mm}^{-2}\text{)} = [\text{Increase in length (mm)/ Original length} \times 100/ \text{ Cross sectional area (mm}^{-2}\text{)}.... \text{ (6)}$$

2.2.9. Flatness assessment

The construction of a film strip cut from a drug loaded matrix film is an indicator of its flatness. Longitudinal strips (1.5 cm × 0.75 cm) were cut out from each film: one film each from the centre, left side, and right side.

The films were kept at room temperature for 1 hr after measuring the initial lengths of films. The change in the length due to non-uniformity in flatness were measured. Flatness of films was calculated by measuring constriction of strips and a zero percent of constriction was considered to be equal to 100% flatness [15].

% construction = L1 –L2/L2 ×100

% construction = Initial length of each strip (cm) - Final length of each strip (cm) /Final length of the strip (cm) ×100

2.2.10. Folding Endurance

The folding endurance was measured manually for the prepared films to assess the strength and flexibility of film. Folding endurance is defined as the number of folds required to break the polymeric film. This was determined by repeatedly folding a small strip of film (5 × 5 cm) at the same place till it broke. The number of time the film could be folded at the same place without breaking/cracking was the folding endurance value of that prepared transdermal film [15].

2.2.11. Preparation of rat abdominal skin for ex-vivo permeation studies

Wistar rats weighing 150-200g were sacrificed using anaesthetic ether. The full thickness abdominal skin was removed and hair was carefully trimmed with electrical clippers. The epidermis was soaked for 30 sec at 60 ° and fatty layer of epidermis was removed carefully. The epidermis was washed with normal water and was used for *ex-vivo* permeation studies [16].

2.2.12. Ex-Vivo permeation studies

Ex-vivo permeation studies were conducted using fabricated Franz diffusion Cell with a surface area of 3.56 cm^2. The prepared rat abdominal skin was cut into desired size and was placed between the receptor and donor compartments of the diffusion cell. The fabricated patch was cut in 3.56 cm^2 and was placed over the skin. The stratumcorrneum side of the skin was kept in intimate contact with the release surface of the films.

The donor compartment was kept on the receptor compartment and kept tightly with the help of clamps. Phosphate buffer saline pH 7.4 was used as the receptor fluid. It was filled into the receptor compartment through the sampling port and checked for the absence of any air bubble under the skin. The entire assembly was kept on the magnetic stirrer. A magnetic bead was placed in the receptor compartment and was rotated at a constant speed for maintaining the hydrodynamics of the fluid constant throughout the study. The temperature of the receptor fluid was maintained at 37 ± 2 °C with the help of thermostat.1.5 mL of sample aliquots was collected at pre-determined time points and was injected into the HPLC system after filtering through 0.25 µm membrane filters and suitably diluting it.

The samples were replaced with the same volume of phosphate buffer saline pH 7.4 to keep the volume of the receptor compartment constant and also to ensure an intimate contact between the dermal surface of the skin and

the receptor solution. Cumulative amounts of drug permeated in µg/cm^2 were calculated and was plotted against time. Drug flux (µg/cm^2/ hr) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface (3.56 cm^2) and the permeability coefficient was calculated by dividing the flux by initial drug loaded as shown in table 4.

2.2.13. Skin irritation studies

Skin irritation studies were performed on healthy rabbits weighing to an average weight of 1.5 to 2.25 kg. The dorsal surface (50cm^2) of the rabbits was cleaned, and the hair was removed by shaving. The skin was cleansed with rectified spirit. A film (NS6 and NSE5) was placed over the skin with the use of adhesive tape and was removed after 24 hrs to check the skin irritation [17].

2.2.14. FTIR Studies

Fourier trasform infrared (FTIR) technique was used to study the physical and chemical interaction between drug and excipients. FTIR spectrum of Nisoldipine, physical mixtures of Nisoldipine: HPMC E-15: Eudragit RS 100 and Nisoldipine: HPMC E-15: Ethyl cellulose was recorded using KBr mixing method on FTIR (FTIR-1700, Shimadzu, Kyoto, Japan). IR spectra are shown in Figures 7 a, b & c.

2.2.15. Stability studies

The stability studies were conducted for the optimized formulations. The films from different formulations were wrapped in aluminium foil and stored in a petri dish at temperature of 40 ± 2 °C, 75 ± 5 % RH for 6 months. The samples were withdrawn at regular interval of 1, 2, 3 and 6 months and analysed for drug content using the HPLC.

3. Results and Discussions

3.1. Formulation of Nisoldipine transdermal films

NSP transdermal films were fabricated employing various concentrations of Ethyl cellulose (EC) or Eudragit ERS 100 and HPMC E-15. The films were fabricated initially with 1: 10 ratio of Drug: polymer. The obtained films were very thin and were getting adhered to the petri plates and it was difficult to remove. The polymer concentration was then increased to 1:20. As the concentration of polymer was increased, films with good thickness were obtained and the films could accommodate required amount of the drug.

The films were pale yellow in colour due to the colour of NSP pure drug. The films were appearing transparent suggesting that the drug was completely dispersed in the polymeric matrix. The weight variation test observations for the fabricated films are shown in table 2. Results indicate the uniformity of weight of the films according to the %RSD values, which is less than 6.

Thickness of the films in the respective series varied from 210±14.2 µm to 225±12.4 µm (NS) and 209±15.3 µm

to 220±14.8 µm (NSE). The results (table 2) suggest that change in polymer concentration did not product any significant change in the thickness of the films.

Table 1 : NSP: Nisoldipine; ; HPMC E15: Hydroxy propyl Methyl cellulose E15;ERS 100: Eudragait RS 100; EC:Ethyl cellulose. Solvent system: 20mL of 1:1 of DCM and Methanol. Plasticizer 15% w/v of propylene glycol. Drug content: 4mg in each film 1.78 x1.78 cm^2

Formulation	Ingredients (Parts)			
	NSP	HPMC E15	ERS 100	EC
NS1	1	…	20	…
NS2	1	5	15	…
NS3	1	7.5	12.5	…
NS4	1	10	10	…
NS5	1	12.5	7.5	…
NS6	1	15	5	…
NSE1	1	…	…	20
NSE2	1	5	…	15
NSE3	1	7.5	…	12.5
NSE4	1	10	…	10
NSE5	1	12.5	…	7.5
NSE6	1	15	…	5

Table 2: Physicochemical properties of fabricated transdermal films of Nisoldipine

Formulation Code	Weight (mg)	Thickness (µm)	Assay (%)
NS1	184 ±4.5	220±14.5	97.8±4.5
NS2	190±5.5	225±12.4	100.2±1.5
NS3	188±5.2	210±14.2	96.4±4.2
NS4	183±4.3	218±12.5	95.1±2.5
NS5	184±5.4	221±14.3	101.1±1.2
NS6	190±5.7	215±10.5	99.9±4.5
NSE1	186±4.3	218±15.2	98.1±2.3
NSE2	189±5.4	220±14.8	97.5±4.1
NSE3	190±5.8	209±15.3	98.0±1.7
NSE4	183±4.7	216±14.6	97.2±2.5
NSE5	185±5.1	220±12.8	99.3±4.3
NSE6	188±4.9	210±12.2	100.2±1.2

The drug content uniformity was found to be good and was represented in table 2. The drug content in films fabricated with HPMC and ERS was ranged from 97.8±4.5 to 101.1±1.2 whereas films fabricated with combination HPMC & EC was ranged from 97.5±4.1 to 100.2±1.2 respectively.

3.2. In-vitro drug release studies

The *in -vitro* release profiles of NSP form the fabricated films were shown in figure 1a and 1b. Formulations NS6 (2440 µg) and NSE5 (2235 µg) showed maximum amount of drug release in the respective series with zero order (r^2> 0.992& 0.997) release kinetics evidenced from the correlation coefficients.

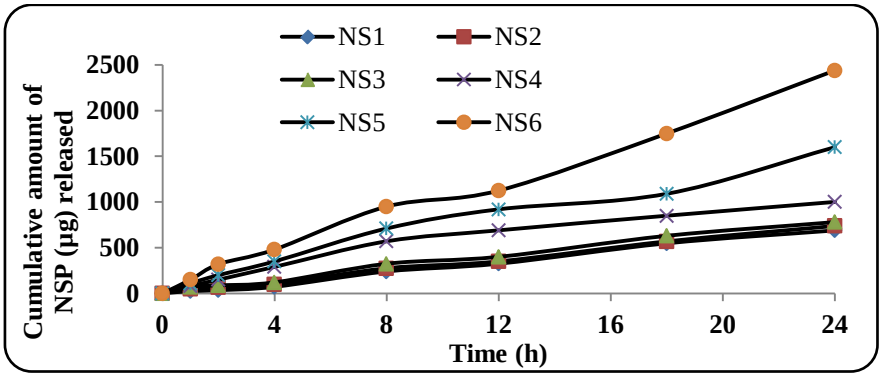

Figure1a: *In -vitro* release profiles of NSP films (NS)

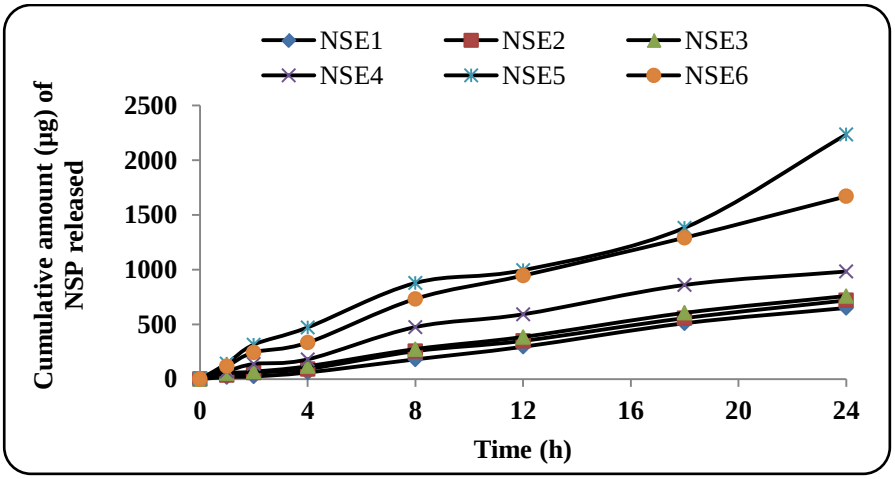

Figure 1b: *In -vitro* release profiles of NSP films (NSE)

The release profiles of the formulations indicate that the drug release from the films is governed by the polymer concentration. As the Hydrophilic polymer concentration increases in the formulations, the rate of drug release increases substantially. The drug release kinetics was calculated for all the formulations and is represented in Table 3. The release exponent (n≥0.50) evidenced non Fickian model of release pattern from optimized formulations.

3.3. Percentage moisture uptake and moisture content

The moisture absorption ranged from 0.05 to 1.74 % in NS series and 0.04 to 1.94 % in NSE series. The moisture content in the films ranged from 0.02 to 0.36 % in NS series and 0.03 to 0.39 % in NSE series and is

represented in Figure 2. The low moisture absorption protects the transdermal films from microbial contamination and small moisture content prevents the films from becoming brittle.

Table 3: in vitro drug release kinetics of NSP transdermal films

Formulation code	Zero order	First order	Higuchi	Peppas Korsemeyar (n)
NS1	0.991	0.994	0.992	0.136
NS2	0.993	0.994	0.993	0.221
NS3	0.994	0.992	0.991	0.136
NS4	0.946	0.961	0.957	0.493
NS5	0.978	0.978	0.981	0.487
NS6	0.992	0.967	0.991	0.552
NSE1	0.994	0.992	0.991	0.420
NSE2	0.996	0.996	0.998	0.079
NSE3	0.997	0.997	0.995	0.027
NSE4	0.975	0.983	0.980	0.441
NSE5	0.97	0.933	0.968	0.552
NSE6	0.991	0.996	0.994	0.578

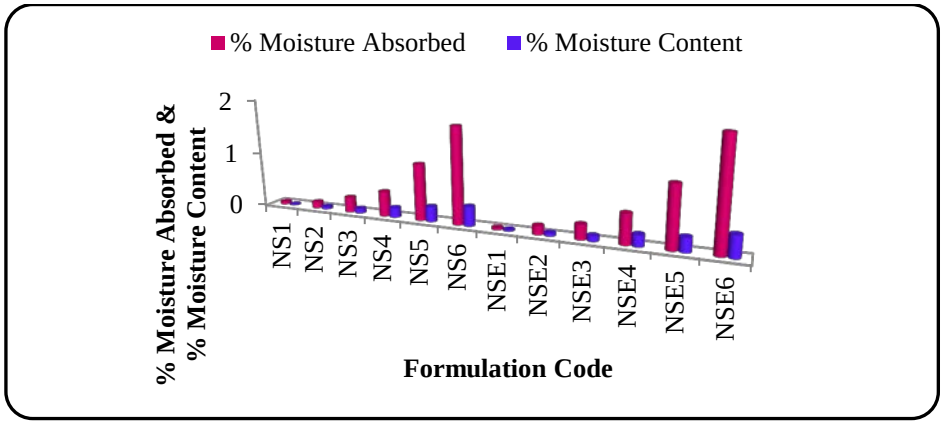

Figure 2: Percentage moisture uptake and moisture content

3.4. Mechanical properties of films

A soft and weak polymer is characterized by low TS and E/B; a hard and brittle polymer is defined by a moderate TS and low E/B; a soft and tough polymer is characterized by a moderate TS and high E/B; where as a hard and tough polymer is characterized by a high TS and E/B [18]. Thus a suitable transdermal film should possess a high TS and E/B.

The results of tensile strength and elongation at break are indicated in the table 3 and figure 3. The formulation.NS1 and NSE4 exhibited greater values of TS (2.6 kg/mm ^{2} and 2.1 kg/mm ^{2} for NS1 and NSE4 respectively). Optimized formulations NS6 (91.4±4.23mm^2) and NSE5 (88.9±10.13 mm^2) showed greater

values of elongation at break in their respective series.

Thus as the concentration of hydrophilic polymer HPMC E-15 increases in NS series the TS decreases and E/B increases. Both TS and E/B found to be increased with increase in concentration of HPMC E-15 in NSE film. The above observations reveal that the formulation NS6 and NSE5films were found to be strong and were not brittle (18).

Table 3: Results of tensile strength and elongation at break of fabricated films

Formulation code	T.S (kg/mm^2)	EB (%mm^2)
NS1	2.6±0.50	16.4±1.38
NS2	1.9±0.22	27.5±2.50
NS3	2.0±0.31	69.2±6.23
NS4	1.4±0.15	86.4±7.98
NS5	1.1±0.11	88.6±5.90
NS6	0.9±0.21	91.4±4.23
NSE1	1.0±0.09	29.8±4.80
NSE2	1.3±0.13	31.6±7.31
NSE3	1.7±0.32	71.0±6.62
NSE4	2.1±0.21	76.7±6.91
NSE5	1.9±0.10	81.2±8.22
NSE6	2.0±0.13	88.9±10.13

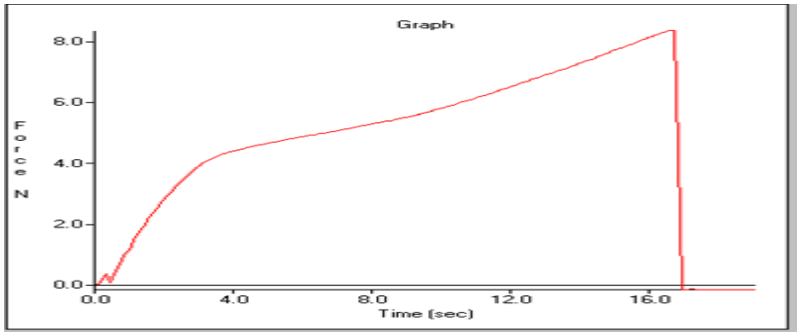

Figure 3: measurement of tensile strength and elongation at break

3.5. Ex-vivo permeation studies of Nisoldipine transdermal films

The results of the *ex-vivo* permeation studies from the NSP films are presented in table 4 and figure 4 & 5.The maximum drug permeation was observed in NS6 and NSE5. The films NS6 (13.03µg/cm^{2}h^{-1}/) and NSE5 (11.77µg/cm^{2}h^{-1}) were considered to be the optimum formulations.

The drug NSP was found to be released from transdermal films and permeated though the rat abdominal skin thus it can could be possibly permeated though the human skin. The permeation pattern was found to be similar with the in vitro release pattern.

Table 4: CR: cumulative amount of NSP released in 24 h; CP: cumulative amount of NSP permeated in 24 h; K: permeability coefficient

Formulation Code	C^{R}_{24} (µg)	C^{P}_{24} (µg)	Flux (µg/cm^{-2}/h^{-1})	K (CM^{-1})
NS1	689	356	5.52	1.38
NS2	738	396	5.76	1.44
NS3	780	456	6.35	1.59
NS4	1001	738	10.45	2.61
NS5	1600	806	10.85	2.71
NS6	2440	953	13.03	3.26
NSE1	650	336	5.33	1.33
NSE2	719	364	5.63	1.41
NSE3	759	640	9.40	2.35
NSE4	983	680	9.93	2.48
NSE5	2235	895	11.77	2.94
NSE6	1670	842	11.43	2.86

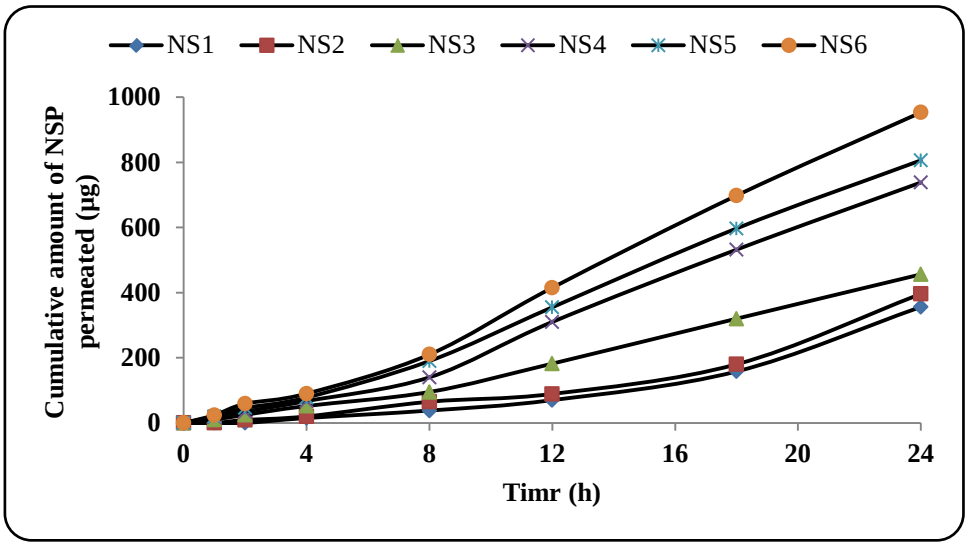

Figure 4 : Ex-vivo permeation profiles of NSP from films fabricated with HPMC E15& ERS10

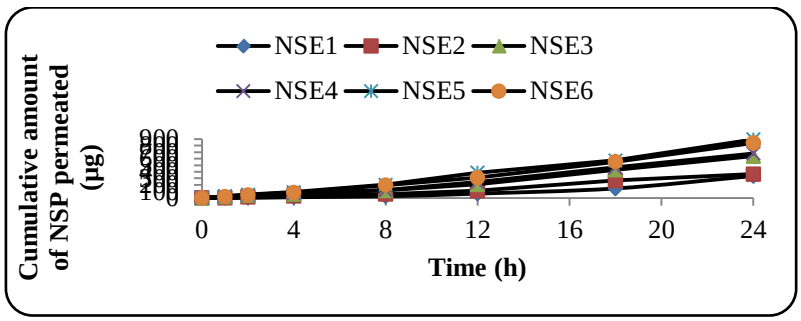

Figure 5: Ex-vivo permeation profiles of NSP from films fabricated with HPMC E15& Ethyl cellulose

3.6. FTIR studies

The FTIR studies shown in Fig.6 indicate no interaction between the drug and polymers. Thus these polymers could be used in sustained/controlled release matrix type tansdedrmal films.

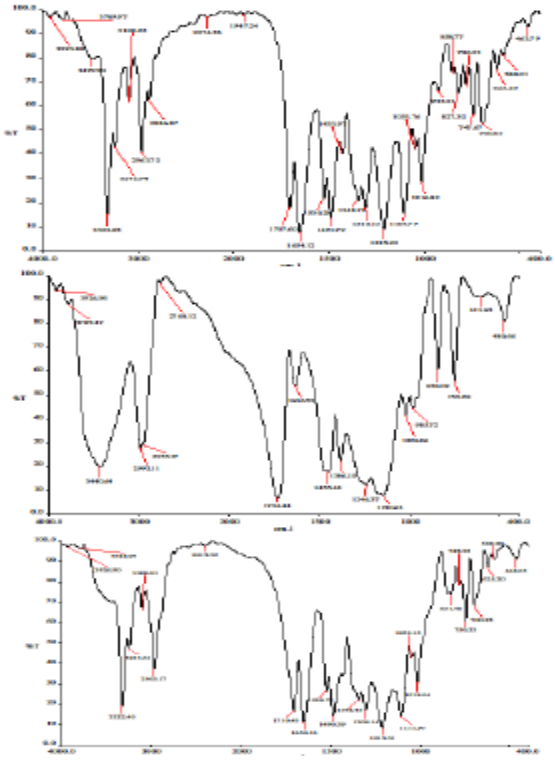

Figure 6: FT-IR Spectra of (i) Nisoldipine (NSP) Pure drug (ii) Physical mixture of NSP+HPMC E15+ERS 100 (iii) Physical mixture of NSP+HPMC E15+Ethyl cellulose

3.7. Stability Studies

The stability studies of the optimized formulations (NS6& NSE5) were carried out as per ICH guidelines. On storing the tansdermal films at 40 ±2°C/75±5% RH for 6 months 1.48% (NS6) and 1.78% (NSE5) degradation was observed. Hence the observed degradation is less than 5 % from initial value in the formulation, a shelf life of 2 years can be proposed.

4. Conclusions

Matrix type transdermal films of NSP could be fabricated with suitable mechanical properties. Further studies could be carried out in human beings for the assessment of pharmacokinetic parameters.

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