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Transdermal Delivery of Felodipine from Eudragit film

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ABSTRACT

Felodipine is an effective calcium channel blocker, mainly used in the treatment of hypertension and angina pectoris. To overcome the low oral bioavailability of felodipine, the present work was designed to develop transdermal therapeutic system for felodipine using the polymer blend of eudragit RL 100 (ERL) / RS 100 (ERS) by solvent casting method. Dibutyl phthalate (DBP) and oleic acid (OA) were used as plasticizer and permeation enhancer respectively. Incorporation of DBP improved the flexibility, folding endurance and handling properties of the films. Increasing the concentration of ERL, and the presence of plasticizer were found to increase the *in vitro* drug release of the films. The patches were also evaluated for *ex vivo* skin permeation using human cadaver skin. The presence of OA produced significant increase in the flux and permeability constant. The formulation with ERL: ERS ratio 4:1, 5% w/w OA as permeation enhancer and 20% w/w DBP as plasticizer showed the best results which exhibited the cumulative percentage of drug release of 75.73 ± 2.179 % and the cumulative amount of drug permeation across skin of 4321 ± 11.533 $\mu\text{g}/\text{cm}^2$ in 24 hrs. Drug-excipient interaction studies were carried out using DSC and IR technique; films indicated no chemical interaction between drug and excipients. The results of the skin irritation studies showed no noticeable irritancy on rabbit skin indicating the skin compatibility of the drug as well as polymer. An attempt was made to develop the complete transdermal system of the drug by using backing membrane and release liner.

Keywords: Transdermal Therapeutic System, Felodipine, Eudragit, Dibutyl Phthalate, Skin Permeation.

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INTRODUCTION

In the recent years, considerable attention has been focused on the development of new drug delivery systems. The therapeutic efficacy and safety of the drugs administered by conventional methods can be improved by more precise spatial and temporal placement within the body, thereby reducing both the size and number of doses through a controlled drug delivery. Among the wide variety of novel controlled drug delivery systems, the transdermal delivery of drugs for the systemic treatment of diseases has acquired increasing interest in recent years due to its potential in avoiding the hepatic first pass effect, thus achieving high systemic bioavailability of drugs and capable of sustaining the drug release for prolonged period of time. Moreover, it provides suitability for self-administration and rapid termination of drug effect if needed, leading to better patient acceptance and compliance^{1,2}.

Transdermal therapeutic systems are ideally suited for diseases that demand chronic treatment. Cardiac disorders such as hypertension, angina pectoris and congestive cardiac failure are the diseases equally prevalent in the developed and the undeveloped countries, demands chronic treatment. Cardiac patients need to be on prolonged medication, and some times life long therapy is advised. Transdermal delivery is considered to be the ideal method for cardiac drugs which can bypass the difficulties of firstpass metabolism, enable absolute elimination of GIT toxic effects, maintain the steady plasma level of drug for a prolonged period and deliver the drug at predetermined rate. Hence, for last two decades, it remained an area of vital research of interest and industries alike to take up challenging projects in this particular arena³.

Felodipine (FD), a potent calcium channel blocker which is widely used in treatment of hypertension & angina pectoris. Although it is rapidly and almost completely absorbed from the GIT, it undergoes extensive first pass metabolism resulting in a bioavailability about 15% after oral administration. Hence to achieve therapeutic concentration, frequent dosing or large doses are required. Large doses can produce bradycardia, hypotension & other adverse effects^{4,5}. Hence to improve bioavailability, therapeutic efficacy, patient compliance and to reduce the frequency of dosing and side effects, TDDS are better suitable for FD.

MATERIALS AND METHODS

Materials

Felodipine was obtained as gift sample from Cipla Ltd. Mumbai. Eudragit RS 100 (ERS) and Eudragit RL 100 (ERL) were procured from Degussa India Pvt. Ltd, Mumbai. Oleic acid (OA), dibutyl phthalate (DBP), methanol and acetone were of analytical grade purchased from Sree

Durga Chemicals, Mangalore. Cellophane membrane was obtained from Sigma Chemicals Co., St. Louis, USA.

Formulation of transdermal patches

The patches were prepared by casting method. A flat square shaped, aluminium foil coated glass molds having surface area 25 cm² were fabricated for casting the patches.

Preparation of Casting Solution

The casting solutions were prepared by dissolving weighed quantities of polymers in acetone-methanol (1:1) mixture. The drug, plasticizer and permeation enhancer were then added to the polymer solution and thoroughly mixed to form a homogeneous mixture. The volume was made up to 7 ml with solvent mixture. Entrapped air bubbles were removed by applying vacuum. Composition of formulation is given in Table 1.

Preparation of Transdermal Patches

Casting solution (5ml) was poured into glass moulds and dried at room temperature for 24 hrs for solvent evaporation. The patches were removed by peeling and cut into square dims of 4 cm x 4 cm (16 cm²). These patches were kept in desiccator for 2 days for further drying and wrapped in aluminium foil, packed in self-sealing covers⁷⁻⁹.

Table 1: Composition of formulations

Code	Polymer ratio ERL/ERS	ERL (mg)	ERS (mg)	FD* (mg)	DBP (mg)	OA (mg)	Acetone -Methanol (1:1) mixture up to (ml)
F1	1:4	140	560	210	-	-	7
F2	2:3	280	420	210	-	-	7
F3	3:2	420	280	210	-	-	7
F4	4:1	560	140	210	-	-	7
F5	4:1	560	140	210	70	-	7
F6	4:1	560	140	210	140	-	7
F7	4:1	560	140	210	210	-	7
F8	4:1	560	140	210	140	17.5	7
F9	4:1	560	140	210	140	35	7

*210mg of felodipine was incorporated in 7ml casting solution. 5 ml of this solution (150mg of felodipine) was spread in to 25 cm² so that each cm² contains approximately 6.0 mg of the drug

Physico-mechanical characterization of transdermal patches

Physical appearance

All the formulated transdermal patches were visually inspected for colour, flexibility, homogeneity and smoothness¹⁰.

Thickness

The thickness was measured at five different places on a single patch using a screw gauge. The

average and standard deviation of five readings was calculated for each batch of the films¹⁰⁻¹².

Weight uniformity

The films of different batches were dried at 60 °C for 4 h before testing. Five patches from each batch having diameter of 1cm² were weighed on a digital balance. The average weight and the standard deviation values were calculated from the individual weights¹².

Folding endurance

Folding endurance was measured manually for the prepared films. A strip of film (2x 2cm²) was cut evenly and repeatedly folded until it broke. The number of times the film could be folded at the same place without breaking was observed^{7,13}.

Tensile strength

The tensile strength and percent elongation of the prepared films were performed using the method developed by Allen *et al*¹⁴. A simple apparatus designed at laboratory was used to carry out the measurement (Figure.1). A strip of 2.5 x 5 mm was selected and attached to a clip on one end of a flat wooden surface. The thread was attached carrying a pan at the other end. The points of attachments were kept 0.5cm from both the sides, so as to get even force distribution and to avoid breaking of film abruptly. The other end of thread carrying the pan was allowed to slide over a pulley opposite to fixed end. Weights were added in the pan in increasing order till the point of break-up. The elongation of the film at the point of break-up was also measured. The tensile strength was calculated as per Alien's formula; Tensile strength = (Break force/a x b) X (1+ Δ L/L), where, a is the thickness, B is the width of the strip of film, Δ L is the elongation at the breaking point and L is the length of the test strip (mm).



Figure 1: Instrument for the measurement of tensile strength of films

Hardness

The apparatus employed for hardness determination was designed in the laboratory using the literature report (Figure .2). It consists of a wooden stand of 11 cm height and top area of 16 cm × 16 cm. A small pan was fixed horizontally to one end of the 2 mm thick iron rod whose other end is reduced to a sharp point. A hole of 0.2 cm was made at the center of top area of a wooden

stand, which was supporting the pan rod. An electric circuit was made with two 1.5-volt battery and a three volt electric bulb in such a way that the bulb lights only when circuit is completed through the contact of a metal plate and sharp end of the rod. The film was placed between the metal plate and sharp end of the rod. The increments of weights were gradually added at an interval of 10 seconds to the surface of wooden plate and when the hardness of the film exceeded, the sharp end penetrates across the film, contact the metal plate and the bulb glows. The average of five such readings was noted at different places of the film and the mean values for the hardness is recorded¹⁴.



Figure 2: Instrument for the measurement of hardness of films

Drug content uniformity

The film of 1cm² area was cut into small pieces and transferred in to a graduated glass stoppered flask containing 20 ml of methanol. The flask was shaken continuously for 24 hrs in a mechanical shaker. Then the solution was filtered and residue was washed with methanol. The filtrate was made up to 100 ml with phosphate buffer pH 7.4 containing 20% v/v PEG 400 and the absorbance was measured at 358.5 nm in a double beam UV spectrophotometer (Systronics-2203) using the placebo film solution as blank and the drug content was determined¹³.

***In-vitro* Drug Release Studies**

In vitro drug release studies were performed by using Keshery - Chein diffusion cell with cellophane membrane. The receptor compartment was filled with 30 ml of phosphate buffer pH 7.4 containing 20% v/v PEG 400 as diffusion media. The prepared transdermal film of 1 cm² was placed in the donor compartment. The whole assembly was fixed on a hot plate magnetic stirrer and the solution in the receptor compartment was continuously stirred at 100rpm using magnetic beads and the temperature was maintained at 37 ± 1°C. 3 ml sample of the receptor fluid were withdrawn at predetermined time intervals and replaced immediately with same volume of fresh diffusion media. The samples were analyzed for drug content at 358.5 nm using UV - visible spectrophotometer (Systronics-2203) after suitable dilution with diffusion media¹⁸.

Ex-vivo Skin Permeation Studies

The *ex vivo* skin permeation study was carried out using human cadaver skin on basis of the study protocol approved by the Institutional Ethical Committee (CPCSEA Reg. No.1564/PO/a/11/CPCSEA-23-1-12). The healthy skin from the forearm region of cadaver brought for autopsy was taken in a sealed evacuated plastic bag in a thermos containing ice. The human skin was freed from fat by the use of Irish scissors till the dermis is seen. The hair was cut and then the skin was allowed to stand at room temperature and rehydrated by immersing in distilled water for 15 minutes. Then the cadaver skin was mounted between donor and receptor compartment of the diffusion cell with epidermis facing towards the donor compartment. 30 ml of phosphate buffer pH 7.4 containing 20% v/v PEG 400 was used as elution medium. The films of 1 cm² were placed in between the donor and the receptor compartment in such a way that the drug releasing surface faced toward the receptor compartment. The elution medium was magnetically stirred for uniform drug distribution at a speed of 100rpm. The temperature of the whole assembly was maintained at 37 ± 1°C by thermostatic arrangements. An aliquot of 3ml was withdrawn at a suitable interval and an equivalent volume of fresh buffer was replaced. The amount of drug permeated across the membrane was determined at 358.5 nm spectrophotometrically after proper dilution with the elution medium. The cumulative amount of drug permeated was calculated and plotted against time¹⁸⁻²⁰.

Estimation of area of patch required for desired release rate

The mathematical description of drug release that follow zero order kinetics is based on the equation; $K_r = K_e \cdot C_d \cdot V_d \cdot BW$ where K_r is rate constant for drug release, K_e is the first order rate constant for drug elimination, C_d is the therapeutic drug concentration, V_d is the volume of distribution and BW is the standard body weight. For felodipine, $t_{1/2} = 12$ h, $C_d = 6.24$ µg/l and $V_d = 10$ l and therefore the desired drug release rate can be calculated as $K_r = (0.693/12) \times 6.24 \times 10 \times 70 = 252.25$ µg/hr. Hence, area of patch (A) required for desired release rate is $A = K_r / (K_p/S)$, where K_r is the required drug release rate (mg/h) and S is the surface area of the film subjected to diffusion (cm²)^{21,22}.

Compatibility Studies

The D.S.C. and I.R. studies were performed to check the compatibility of drug and polymers. Spectra of the pure FD, ERS, ERL and the formulated film (F9) were taken individually the peaks were compared for any significant deviation.^{23,24}

Stability Study

The stability studies of the formulated transdermal patches were carried out on selected films

(F9) as per ICH guidelines. The patches were wrapped in aluminium foil and stored at $40 \pm 0.5^{\circ}\text{C}$ and $75 \pm 5\%$ RH for 3 months. The sample patches were withdrawn at 0, 30, 60 and 90 days and analysed for the drug content and drug releasing characteristics^{24,25}.

Primary Skin Irritancy Studies

Patches were applied to the shaved skin on one side of the back of rabbit and secured using adhesive tape. On other back side of the rabbit, control patch (without drug) was secured in a similar way. The animal was observed for any sign of erythema or oedema for a period of 48 hours^{7,16}.

Lamination of Transdermal Patch

In view of the limited usefulness of the film (Figure. 3) to the patient, an attempt has been made to develop the complete transdermal therapeutic system of the drug by using backing membrane and release liner (Figure. 4). The transdermal patch of 1cm diameter was cut and placed on an aluminium foil of 1.3 cm diameter that serves as the backing membrane. A solution of polyisobutylene was applied along the circumference of the aluminium foil and dried at room temperature for 10 hrs. The patch was covered with silicone coated release liner¹⁸.



Figure 3: Prepared transdermal film

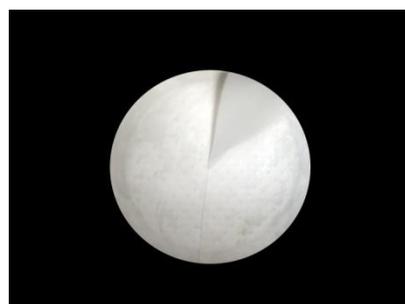


Figure 4: Laminated transdermal patch

RESULTS AND DISCUSSION

Physico-mechanical characterization

In the present study, total nine patches were formulated by varying polymer (ERS / ERL) ratio, plasticizer and permeation enhancer concentration. In all these formulations a constant amount of drug (210 mg) was maintained. 5 ml of the casting solution was spread in to 25 cm^2 so that each cm^2 contains approximately 6.0 mg of the drug. The prepared films were slightly pale yellow coloured with homogeneous appearance and possessed uniform surface. Drug was uniformly distributed through the matrix film. There were no observable particles of drug in the matrix film. The physicommechanical valuation data of the films was presented in Table 2.

The folding endurance was measured manually and it is found that ERL / ERS films without adjuvants were hard, brittle and fragile with low folding endurance. To prevent embrittlement, a

plasticizer, DBP was tried at various concentrations: 10 % w/w, 20 % w/w and 30% w/w in respect to the dry weight of the polymer. The plasticizer can diffuse in to and softens the polymer matrix. Folding endurance value were 78 ± 1.93 for formulation F1 and 204 ± 2.07 for formulation F9, other formulations were within these ranges, which shown that hydrophilic polymer (ERL) and the presence of plasticizer can provide higher folding endurance and good flexibility. The results suggested that the patches would not break and would maintain their integrity with general skin folding when applied. However, the film with 30% w/w of DBP was not satisfactory because of its sticky nature.

The films were evaluated for the film thickness at various points. It was found that the thickness at the edges of the rectangular tray was a bit higher and uneven compared to the rest of the parts of the film. It may be due to the curvature of the viscous slurry at the edges of the foil due to surface tension. After removing these edges, films were remeasured for thickness and it was observed to have uniform thickness and low standard deviation. It indicates the uniformity of the films prepared by the solvent casting method. The thickness was found to be high with films prepared with DBP as plasticizer. As the proportion of DBP was increased, the thickness was also increased (Table 2).

Table 2: Physico-mechanical characters of formulated transdermal films

Code	Thickness (mm)	Weight (mg)	Folding Endurance	% Elongation at break	Tensile strength (Kg/cm ²)	Hardness (Kg)
F1	0.209 ±0.020	26.647 ±0.154	78 ± 1.93	6.8 ±1.541	0.349 ±0.066	0.438 ±0.047
F2	0.213 ±0.025	27.232 ±0.208	94 ± 1.51	8.2 ±1.164	0.362 ±0.073	0.423 ±0.032
F3	0.206 ±0.031	27.784±0.177	112 ± 2.05	8.7 ±1.275	0.375 ±0.051	0.396 ±0.065
F4	0.214 ±0.022	28.323 ±0.251	119 ± 2.48	9.5 ±1.845	0.389 ±0.012	0.387 ±0.071
F5	0.226 ±0.012	30.492±0.208	167 ± 1.44	17.4 ±2.075	0.422 ±0.070	0.384 ±0.019
F6	0.235 ±0.016	32.647 ±0.152	192 ± 2.35	21.5 ±2.204	0.476 ±0.045	0.373 ±0.026
F7	0.242 ±0.022	34.995 ±0.284	132 ± 3.67	27.1 ±2.516	0.565 ±0.098	0.332 ±0.035
F8	0.243±0.012	33.931 ±0.173	196 ± 1.92	22.4 ±2.081	0.499 ±0.036	0.376 ±0.029
F9	0.245 ±0.010	34.267 ±0.157	204 ± 2.07	23.9 ±1.947	0.527 ±0.053	0.375 ±0.057

No significant difference in the average weight among each group indicating that the patches are uniform throughout. However the average weight of the patches was slightly increased with hydrophilic polymer ERL. The increase in the weight may be due to the hydrophilic nature of the adjuvants which may absorb moisture from the atmosphere resulting in increase in weight. It was also found that, with the incorporation of hydrophilic polymer, ERL and plasticizer, DBP, were increased the tensile strength and the percentage elongation where as the hardness of the film decreased, but, the incorporation of OA as permeation enhancer at 2.5% w/w and 5 % w/w did not affect significantly the physicommechanical and handling properties of the film.

Good uniformity of the drug content among the patches was observed for all the formulations which ranged from 94.75% to 98.42% (Table 3). Based on the initial drug loading, all the formulations were containing above $5.685 \pm 0.0217\text{mg}$, which proves that the process employed to prepare the films in this study was capable of producing films with uniform drug content and minimum batch variability.

Table 3: Drug content of prepared transdermal films

Formulation Code	Amount of drug (1cm^2) (mg) AM \pm SD	Percentage of drug (1cm^2)AM \pm SD
F1	5.716 ± 0.0349	95.278 ± 0.5704
F2	5.749 ± 0.0343	95.827 ± 0.5679
F3	5.837 ± 0.0338	97.283 ± 0.5678
F4	5.734 ± 0.2667	95.556 ± 0.4556
F5	5.851 ± 0.0515	97.517 ± 0.8585
F6	5.773 ± 0.0536	96.222 ± 0.9298
F7	5.685 ± 0.0217	94.755 ± 0.3534
F8	5.691 ± 0.0381	94.844 ± 0.6609
F9	5.828 ± 0.0387	97.133 ± 0.6435

***In-vitro* drug release**

In-vitro drug release studies from transdermal patches were carried out through cellophane membrane and the results are summarized in Figures 5 and 6. It was observed that, as the concentration of ERL increased, the percentage of drug release also increased. More permeability of these films may be due to its hydrophilic nature, which increases the porosity and diffusivity of the film and thermodynamic activity of the drug. The release pattern of FDP was found to be enhanced significantly when DBP was incorporated to the films as plasticizer, It is indicated that the drug release rate increased gradually as the amount of DBP was increased. The results suggest that ERL and DBP had major influence on drug release.

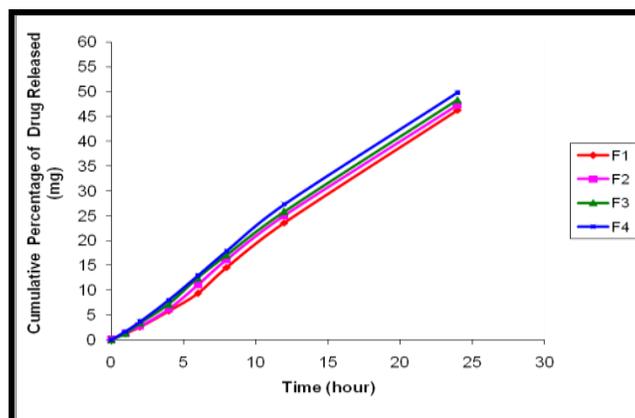


Figure 5: Effect of polymer composition (ERL/ERS) on the *in-vitro* drug release of formulated transdermal films(F1 to F4)

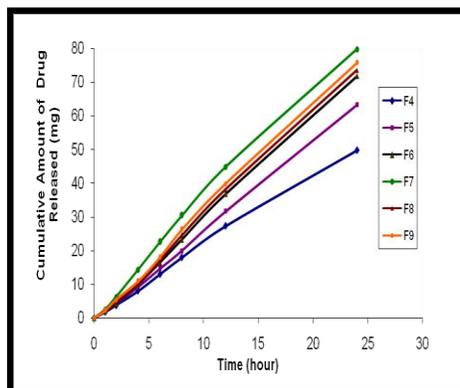


Figure 6: Effect of the concentration of plasticizer (DBP) and permeation enhancer (OA) on the *in-vitro* drug release (F4 to F9)

The rate and mechanism of release of felodipine were analysed by fitting the drug release data in to zero order equation, first order equation, Higuchi and Korsmeyer-Peppas models. The cumulative amount of drug released from the patches, when plotted against time, the release profiles of drug seemed to follow zero order as it was evidenced by correlation coefficients ($r^2 = 0.97$ to 0.99) better than Higuchi model ($r^2 = 0.95$ to 0.97) and first order ($r^2 = 0.53$ to 0.56).

***Ex-vivo* drug permeation**

The *ex-vivo* permeation of the drug through human cadaver skin was slightly lesser than cellophane membrane. However, the incorporation of OA can significantly improve the drug permeation characteristics through human cadaver skin. (Figure.7 and 8). Incorporation of OA into the polymer disturbs the continuity of the polymer chains, thereby decreasing molecular order and increasing the chain mobility of the polymer matrix. As a consequence, permeability enhanced which results in increased drug release.

The *in vitro* drug release and *ex vivo* skin permeation studies revealed that the combined use of plasticizer and permeation enhancers increased the release rate and amount of the drug from the patches compared to that of their single use. The incorporation of DBP in to the FD-eudragit films may be useful for improving the physico-mechanical and drug release properties of the films and the incorporation of OA into the films may be useful for attaining required drug permeation. Thus, the film-F9 with ERL: ERS ratio 4:1, 5% w/w OA as permeation enhancer and 20% w/w DBP as plasticizer showed the best results which exhibited the cumulative percentage of drug release of 75.73 ± 2.179 % and the cumulative amount of drug permeation across skin of 4321 ± 11.533 $\mu\text{g}/\text{cm}^2$ in 24 hrs. The transdermal flux, permeability coefficient and area of the film required for desired release rate for the transdermal film-F9 were calculated and are reported in Table 4.

Table 4: Transdermal flux, permeability coefficient and area of the required for desired release rate for the transdermal film-F9

Parameters	F9 Film
Cumulative % of drug released - 24 hr	75.73 %
Cumulative amount of drug permeated through skin - 24 hr	4321.2 $\mu\text{g}/\text{cm}^2$
Lag time	0.8 hr
Transdermal flux	187.97 $\mu\text{g}/\text{hr}/\text{cm}^2$
Permeability coefficient	3.13 $\times 10^{-2}$ cm^2/hr
Targeted flux	252.25 $\mu\text{g}/\text{hr}$
Area of film required for TDDS	1.342 cm^2

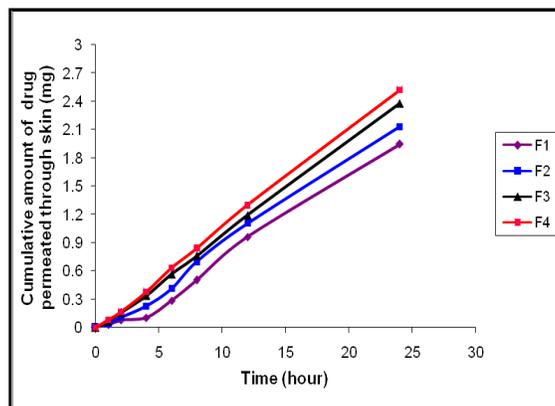


Figure 7: Effect of polymer composition (ERL/ERS) on the *ex-vivo* skin permeation of drug from transdermal films (F1 to F4)

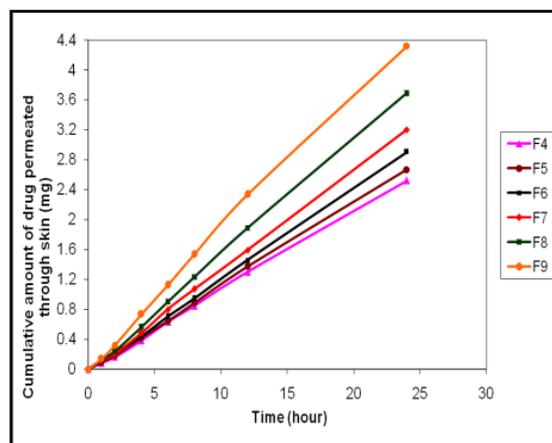


Figure 8: Effect of the concentration of plasticizer (DBP) and permeation enhancer (OA) on the *ex-vivo* skin permeation of drug from transdermal films (F4 to F9)

Compatibility

The D.S.C. and I. R. studies revealed that there was no significant change in the original peak of the drug and the polymers after formulating the patch(Figure.9 -12), indicating that there is no interaction between drug and polymers.

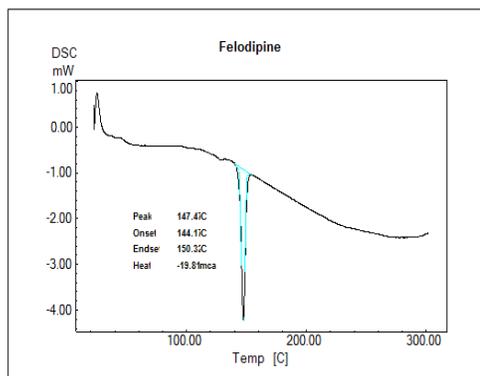


Figure 9: D.S.C of Felodipine (pure drug)

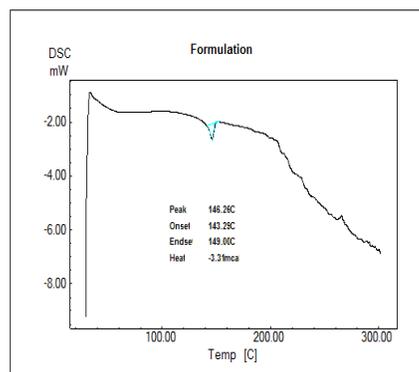


Figure 10: D.S.C of Transdermal film- F9

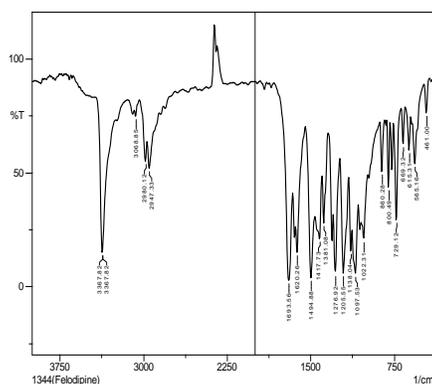


Figure 11: FTIR spectra of Felodipine

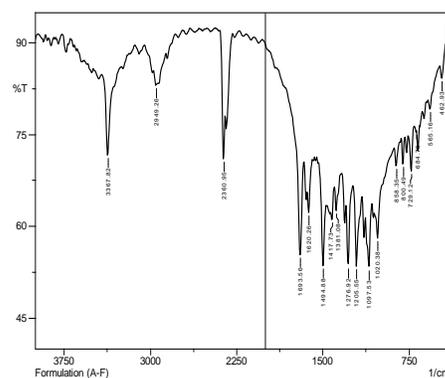


Figure 12: FTIR spectra of Transdermal film- F9

Stability

Stability studies were carried out for 6 months and the films were observed for various physico-mechanical and drug release characteristics. It was found that, there is no significant change in physical appearance, thickness, weight, folding endurance and tensile strength and drug content (Figure.5). Drug release and permeation characteristics did not alter significantly even after 3 months storage.

Table 5. Stability testing of the transdermal film-F9

Parameters	0 Day	After 90 Days storage
Thickness	0.245 ± 0.010 mm	0.236 ± 0.0175 mm
Weight	34.267 ± 0.157 mg	34.212 ± 0.643 mg
Folding Endurance	204 ± 2.07	198 ± 3.62
Tensile Strength	0.527 ± 0.053 Kg/cm ²	0.539 ± 0.028 Kg/cm ²
Hardness	0.375 ± 0.057 Kg	0.351 ± 0.095 Kg
Drug Content	5.828 ± 0.038 mg/cm ²	5.789 ± 0.047 mg/cm ²
CDR at 24hrs	75.73%	75.85%

Skin irritancy

Results of skin irritancy study revealed that neither blank patch nor patch containing FD cause any noticeable sign of erythema or oedema on rabbit skin throughout the period of 48 hrs,

indicating the skin compatibility of blank patch as well as patch containing drug.

CONCLUSION

Based on the physico-mechanical and drug release characteristics, ERL 100/RS 100 (4:1) films with DBP (20% w/w) and OA (5% w/w) are suitable to design matrix dispersion type transdermal films for FDP. The fabricated transdermal delivery system containing FDP is one of the best controlled drug delivery systems in the effective therapy and prophylaxis of hypertension, angina pectoris and cardiac arrhythmia, where the drug is made available for an extended period of time, so frequency of administration can be minimized. The film composition and additives can be optimized to get the release over prolonged period of time as once a week or once a month transdermal formulations. Further, these findings may help the industry to scale up for commercial production.

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