

IN-VITRO, EX-VIVO AND IN-VIVO EVALUATION OF TRANSDERMAL DELIVERY OF FELODIPINE

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ABSTRACT

Felodipine, an effective calcium channel blocker, widely used for the treatment of chronic stable angina and hypertension seems to be potential therapeutic transdermal system candidate, mainly due to its low oral bioavailability, short half life and high first-pass metabolism. Hence an attempt was made to develop transdermal therapeutic systems for felodipine using the polymer blend of eudragit RL100 (ERL) and hydroxypropyl methylcellulose (HPMC) by casting method and to study the effect of polymer composition, plasticizer and permeation enhancer on the physico-mechanical and *in vitro* drug release characteristics of the film. Polyethylene glycol 400 (PEG 400) and span 60 were used as plasticizer and permeation enhancer respectively. Incorporation of HPMC and PEG 400 improved the flexibility, folding endurance and handling properties and *in vitro* drug release of the films. The patches were also evaluated for *ex vivo* skin permeation using human cadaver skin. The presence of span 60 produced significant increase in the flux and permeability. The formulation with ERL:HPMC ratio 2:3, 4% w/w span 60 as permeation enhancer and 7.5% w/w PEG 400 as plasticizer showed the best results which exhibited the cumulative percentage of drug release of 84.96% and the cumulative amount of drug permeation across skin of 4861.4 μ g/cm² in 24 hrs. *In vivo* studies of this transdermal system in rabbits demonstrated a four fold enhancement of bioavailability of felodipine relative to oral administration. It may be concluded that the fabricated transdermal delivery system have the potential to provide controlled and extended drug release, better bioavailability and thus, they may improve the patient compliance.

Keywords: *Transdermal delivery system; Felodipine; Eudragit; HPMC; Skin Permeation.*

INTRODUCTION

Felodipine (FD) a potent calcium channel blocker, widely used in the treatment of hypertension and angina pectoris. However, the literature survey reveals that, it undergoes variable and extensive first pass metabolism following oral administration resulting in oral bioavailability of about 15%¹. Hence to achieve therapeutic concentration, frequent dosing or large doses are required. But the oral administration of large dose of felodipine can produce nausea and other gastro-intestinal disturbances². Hence, to improve the bioavailability, transdermal drug delivery systems (TDDS) are better suited for felodipine. Moreover, felodipine is an ideal candidate for the transdermal delivery because of its low molecular weight (384.3D), low dose (5-10 mg/day) and balanced hydrophilic-lipophilic characteristics (log P = 3.86)^{3,4}.

Transdermal delivery of felodipine avoids the firstpass effect and provides greater and more prolonged levels of unchanged felodipine compared to the oral regimen and overcomes the problems associated with oral administration of the drug. In addition, patient compliance, convenience of application and removal,

reduced frequencies of drug dosing are some more advantages with TDDS^{4,5}.

In present study, matrix diffusion controlled TDDS was designed and developed for extended delivery of felodipine using hydrophilic-lipophilic polymer combination. Even though various techniques are reported in the literature, the matrix diffusion controlled TDDS was selected because of ease of fabrication⁶.

EXPERIMENTAL

Materials

Felodipine was obtained as gift sample from Cipla Ltd. Mumbai. Eudragit RL100 (ERL) was procured from Degussa India Pvt. Ltd, Mumbai. Hydroxypropyl methylcellulose (HPMC), Polyethylene glycol 400 (PEG 400), span 60, methanol and acetone were of analytical grade and purchased from Sree Durga Chemicals, Mangalore. Cellophane membrane was obtained from Sigma Chemicals Co., St. Louis, USA.

Fabrication of transdermal patches

The patches were prepared by casting method. A flat square shaped, aluminium foil coated glass molds

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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 (ERL and HPMC) in acetone-methanol (1:1) mixture. The drug (FD), plasticizer (PEG 400) and permeation enhancer (span 60) 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.

Table 1: Composition of formulations

F. Code	Polymer ratio ERL/ HPMC	ERL 100 (mg)	HPMC (mg)	FD (mg)	PEG 400 (mg)	Span 60 (mg)	Methanol - Acetone (1:1) Mix. 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	2:3	280	420	210	17.5	-	7
F6	2:3	280	420	210	35	-	7
F7	2:3	280	420	210	52.5	-	7
F8	2:3	280	420	210	52.5	14	7
F9	2:3	280	420	210	52.5	28	7
F10	2:3	280	420	210	52.5	42	7

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) (Fig. 1). These patches were kept in desiccator for 2 days for further drying and wrapped in aluminium foil, packed in self-sealing covers⁷⁻⁹.

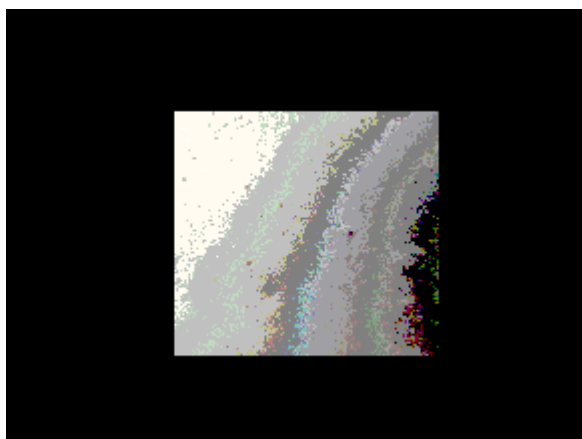


Fig. 1: Prepared transdermal film

Lamination of Transdermal Patch

The prepared transdermal patch was cut and placed on an aluminium foil that served as the backing membrane. 5% w/v solution of poly isobutylene was applied as adhesive along the circumference of the aluminium foil and dried at room temperature for

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10 hrs. The patch was covered with silicone coated release liner¹⁰ (Fig. 2).

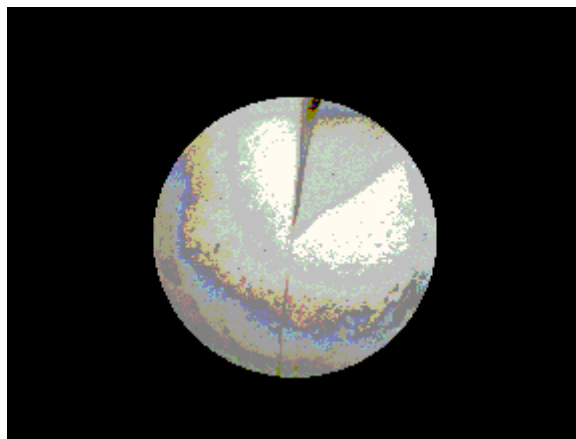


Fig. 2: Laminated transdermal patch

Physico-mechanical characterization of transdermal patches

Physical appearance

All the formulated transdermal patches were visually inspected for colour, flexibility, homogeneity and smoothness¹¹.

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 films¹¹⁻¹³.

Weight uniformity

The films of different batches were dried at 60°C for 4 hrs before testing. Five patches from each batch having area of 1 cm² were weighed on a digital balance. The average weight and the standard deviation values were calculated from the individual weights¹³.

Folding endurance

Folding endurance was measured manually for the prepared films. A strip of film (2 x 2 cm²) 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^{7,14}.

Tensile strength

The tensile strength and percent elongation of the prepared films were performed using the method developed by Allen *et al*¹⁵. A simple apparatus designed at laboratory was used to carry out the measurement (Fig. 3). 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 0.5 cm from both the sides, so as to get even force distribution and to avoid breaking of film abruptly. The other end of thread

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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 Allen's formula:

Tensile strength = (Break force/a x b) X (1 + $\Delta L/L$), where, a is the thickness, b is the width of the strip of film, ΔL is the elongation at the breaking point and L is the length of the test strip (mm)¹⁵.

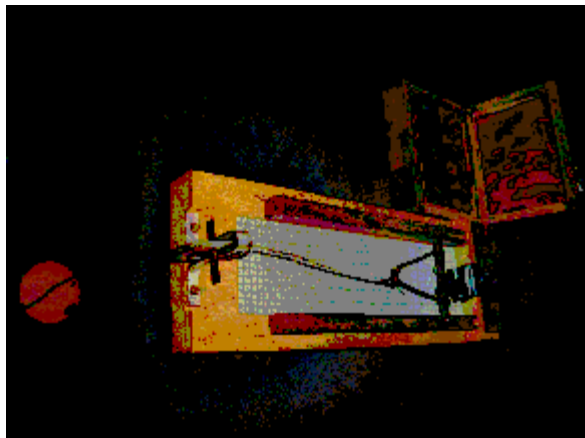


Fig. 3: Instrument for the measurement of tensile strength of film

Drug content uniformity

The film of 1 cm² area was cut into small pieces and transferred into a graduated glass stopper 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 blank film solution as blank and the drug content was determined¹⁴.

In-vitro Drug Release Studies

In vitro drug release studies were performed by using modified 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 for the proper dissolution of the lipophilic drug in receptor compartment. 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

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content at 358.5 nm using UV-visible spectrophotometer (Systronics-2203) after suitable dilution with diffusion media^{10,16}.

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 film of 1 cm² was applied on the epidermal surface of the skin with a pressure sensitive adhesive in such a way that the drug releasing surface faced toward the skin. The elution medium was magnetically stirred for uniform drug distribution at a speed of 100 rpm. 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 time^{17,18}.

In-vivo Skin Permeation Studies

On the basis of the physico-mechanical characteristics, *in-vitro* drug release and *ex-vivo* skin permeation study, the transdermal film-F9 was selected for *in-vivo* performance studies.

Selection of animals

The *in vivo* performance of felodipine following oral and transdermal administration was studied on basis of the study protocol approved by the Institutional Ethical Committee (CPCSEA Reg. No.1564/PO/a/11/CPCSEA-23-1-12) and was based on two-way cross over design. Six healthy rabbits (New Zealand white) of either sex having the weight of 2.8-3.2 Kg were chosen for the study. They were divided into two groups (n=3), and both the products (oral solution and transdermal film) were administered to each group in two different study periods. Before the second study period, an appropriate wash out period of 1 week time was allowed for the drug to be virtually eliminated. Animals were fasted 12 hrs prior to the administration of the drug formulation and until 12 hrs post dosing but

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had free access to water during the entire study period. One day before the experiment, the hair on the abdominal area was removed by applying depilatory for 10 min and washed with distilled water. To study the oral pharmacokinetics, 0.75 mg of FD was administered as solution in distilled water with 20% v/v PEG 400 to rabbits (n=3) using an oral catheter. The catheter was flushed with 5 ml of distilled water with 20% v/v PEG 400 to ensure complete dosing. The remaining rabbits (n=3) were applied 0.125 cm² (0.50cm x 0.25cm) of transdermal film-F9 containing 0.75 mg of felodipine on the hair free abdominal skin with a pressure sensitive adhesive and occluded with plaster^{19,20}.

Estimation of felodipine in serum

About 2 ml of blood samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hrs for oral dose 0, 2, 4, 6, 8, 12, 24, 36, 48 hrs after transdermal administration from the marginal ear vein of the animals into sterilized glass tubes. The serum was separated by centrifugation at 2000-3000 rpm for 10 minutes. The plasma samples were stored at cold temperature until analysis. Safety was evaluated by monitoring adverse events, vital signs and physical examinations.

The method reported by Sreedevi V *et al.*,²¹ was followed for the estimation of felodipine in serum. A volume of 0.5 ml of serum was pipetted into 2.0 ml centrifuge tube and to this 0.5 ml of precipitating agent (10% perchloric acid) was added. The resulting solution was vortexed for 5 min and centrifuged at 4000 rpm for 10 min. Supernatants from the above solutions was separated and filtered using 2 micron pall syringe filter which was then used for the estimation. Analysis was performed using Agilent-1120 IC Compact HPLC which consists of binary pump, rheodyne manual injector, 20 µl sample loop and UV detector. Column used for the analysis was Zorbax C18 Column (250 X 4.6 X 5 mm). HPLC grade methanol and millipore water (80:20) was used as mobile phase. The mobile phase was filtered using 45 micron pall nylon membrane. Sample volume taken is 20 µl and the flow rate was set to 1 ml/min at ambient temperature. Run time was 15 min and the sample was detected at 267 nm. Linearity was evaluated over felodipine concentration range 1 to 60 µg/L in serum with minimum detection limit of 1 µg/L^{21,22}.

Pharmacokinetic analysis

Pharmacokinetic parameters such as maximum serum concentration (C_{max}) and time of its occurrence (t_{max}) were read directly from the individual serum concentration-time profiles. The other pharmacokinetic parameters like biological half life (t_{1/2}), mean residence time (MRT) and area under the curve (AUC) were assessed with KINETIKA 0.5 software, which measures the t_{1/2} from the regression of the terminal phase of

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concentration-time plot. AUC was calculated by linear trapezoidal rule and MRT was calculated by dividing the AUMC by AUC. The results of *in vivo* studies were statistically evaluated using unpaired t-test at 5 % level of significance²³.

RESULT AND DISCUSSION

Physico-mechanical characterization

In the present study, total ten patches were formulated by varying polymer (ERL/ HPMC) 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 cm² so that each cm² 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 physicomachanical valuation data of the films is presented in Table 2.

Table 2: *Physico-mechanical characteristics of formulated transdermal films*

F. Code	Physical Appearance	Thickness (mm)	Weight (mg)	Folding Endurance	Tensile strength (Kg/cm ²)
F1	Tough & Fragile	0.183 ± 0.0037	28.32 ± 0.735	70 - 80	0.291 ± 0.0056
F2	Tough & Fragile	0.176 ± 0.0045	27.94 ± 0.387	50 - 60	0.286 ± 0.0068
F3	Tough & Fragile	0.173 ± 0.0028	27.32 ± 0.662	20 - 30	0.254 ± 0.0087
F4	Tough & Fragile	0.166 ± 0.0052	26.73 ± 0.764	20 - 30	0.242 ± 0.0046
F5	Flexible & Nonsticky	0.182 ± 0.0035	28.82 ± 0.821	110 - 120	0.315 ± 0.0039
F6	Flexible & Nonsticky	0.183 ± 0.0036	29.51 ± 0.592	150 - 160	0.344 ± 0.0066
F7	Flexible & Nonsticky	0.185 ± 0.0056	30.68 ± 0.494	190 - 210	0.372 ± 0.0041
F8	Flexible & Nonsticky	0.186 ± 0.0039	31.24 ± 0.456	200 - 220	0.376 ± 0.0068
F9	Flexible & Nonsticky	0.186 ± 0.0044	31.77 ± 0.554	220 - 240	0.380 ± 0.0071
F10	Sticky & Fragile	--	--	--	--

The folding endurance was measured manually and it was found that ERL / HPMC films without adjuvants were hard, brittle and fragile with low folding endurance. To prevent embrittlement, a plasticizer, PEG 400 was tried at three concentrations: 2.5%, 5%w/w and 7.5% w/w in respect to the dry weight of the polymer. The plasticizer can diffuse into and softens the polymer matrix. Folding endurance value were 20-30 for formulation F3 and F4 and 220-240 for formulation F9, other formulations were within these ranges, which show that hydrophilic polymer (HPMC) 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 applied²⁴. However, the F10 film with 7.5% w/w of PEG 400 and 6% w/w of span 60 was not satisfactory because of its sticky and fragile nature.

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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 method⁹. The thickness was found to be high with films prepared with PEG 400 and span 60. As the proportion of these adjuvants increased, the thickness was also increased (Table 2). 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 HPMC. 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 weight²⁵. It was also found that, with the incorporation of hydrophilic polymer, HPMC, PEG 400 and span 60 the tensile strength and the percentage elongation were increased.

Good uniformity of the drug content among the patches was observed for all the formulations which ranged from 95.33% to 100.26% (Table 3). Based on the initial drug loading, all the formulations were containing above 5.722 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

F. Code	Amount of drug (1cm ²) (mg)	Percentage of drug content (1cm ²)
F1	5.956 ± 0.0256	99.27 ± 0.418
F2	5.873 ± 0.045	97.88 ± 0.75
F3	5.870 ± 0.036	97.83 ± 0.68
F4	5.722 ± 0.0173	95.33 ± 0.288
F5	6.016 ± 0.025	100.26 ± 0.41
F6	5.992 ± 0.0264	99.83 ± 0.447
F7	5.916 ± 0.0208	98.67 ± 0.346
F8	5.887 ± 0.048	98.12 ± 0.81
F9	5.933 ± 0.031	98.8 ± 0.52

In-vitro drug release studies

In-vitro drug release studies from transdermal patches were carried out through cellophane membrane and the results are summarized in Figures 4 and 5. It was observed that, as the concentration of HPMC 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 FD was found to be enhanced

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significantly when PEG 400 was incorporated to the films as plasticizer, it is indicated that the drug release rate increased gradually as the amount of PEG 400 was increased. The results suggest that HPMC and PEG 400 had major influence on drug release¹².

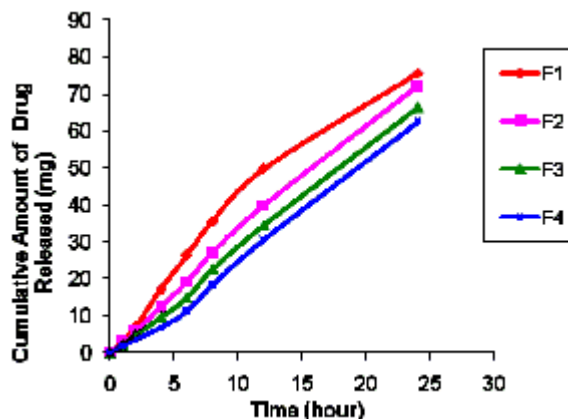


Fig. 4: Effect of polymer composition (ERL/HPMC) on the in-vitro drug release of formulated transdermal films (F1 to F4)

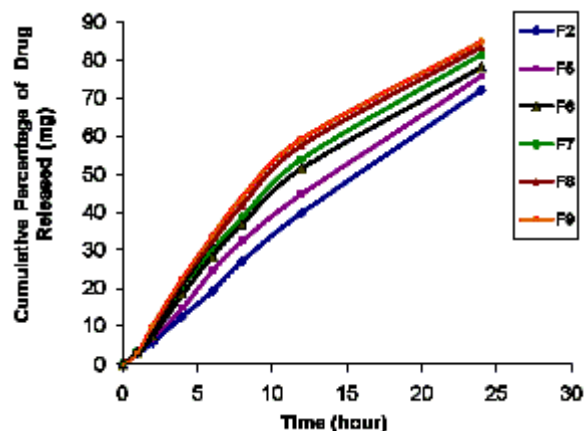


Fig. 5: Effect of the concentration of plasticizer (PEG 400) and permeation enhancer (Span 60) on the in-vitro drug release (F2 & F4 to F8)

Ex-vivo drug permeation studies

The *ex-vivo* permeation of the drug through human cadaver skin was slightly lesser than cellophane membrane. However, the incorporation of span 60 can significantly improve the drug permeation characteristics through human cadaver skin (Fig.6 and 7). Incorporation of span 60 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.

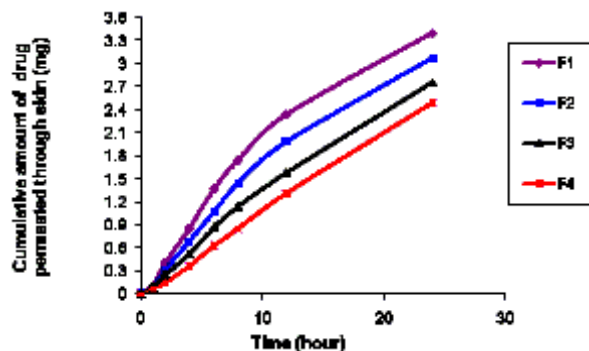


Fig. 6: Effect of polymer composition (ERL/HPMC) on the ex-vivo skin permeation of drug from transdermal films (F1 to F4)

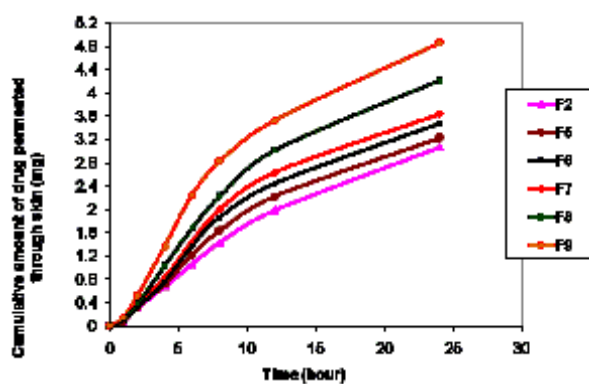


Fig. 7: Effect of the concentration of PEG 400 and Span 60 on the ex-vivo skin permeation of drug from transdermal films (F2 to F4 to F8)

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 PEG 400 into the FD-ERL-HPMC films may be useful for improving the physico-mechanical and drug release properties of the films and the incorporation of span 60 into the films may be useful for attaining required drug permeation. Thus, the film-F9 with ERL:HPMC ratio 4:1, 7.5% w/w PEG 400 as plasticizer and 4% w/w span 60 as permeation enhancer showed the best results which exhibited the cumulative percentage of drug release of 84.96% and the cumulative amount of drug permeation across skin 4861.4 $\mu\text{g}/\text{cm}^2$ in 24 hrs.

In-vivo Skin Permeation Studies

The *in vivo* performance of felodipine following the administration of selected transdermal film-F9 was studied and compared with that of oral administration. FD was not present in the samples taken prior to dosing. These samples served as negative control for the experiment. The results from the oral administration of felodipine solution indicated that it is rapidly absorbed from the gastro-intestinal tract of rabbit having a C_{max}

of $20.5 \pm 1.893 \mu\text{g}/\text{L}$ and t_{max} of 1.5 hr. Transdermal administration of film-F9 achieved almost steady state serum concentration of FD between 17.33 ± 1.886 and $12.50 \pm 1.361 \mu\text{g}/\text{L}$ up to 24 hrs after an initial lag time of approximately 5 hrs (Fig. 8). The low C_{max} and prolonged t_{max} after the administration of transdermal film was due to the barrier properties of the skin and accumulation of the drug in skin tissues in the initial stages followed by continuous delivery in to systemic circulation. After the removal of the transdermal film, a mild reservoir effect was observed for about 3 hrs, followed by normal elimination similar to that after oral administration. This reservoir effect might be due to the slow depletion of the drug accumulated in the skin tissues. The oral administration of FD solution resulted in a low $\text{AUC}_{(0-1)}$ of $146.845 \pm 15.240 \mu\text{g}\cdot\text{hr}/\text{L}$, where as the transdermal administration resulted in $\text{AUC}_{(0-1)}$ of $504.378 \pm 81.402 \mu\text{g}\cdot\text{hr}/\text{L}$. Similarly the mean residence time after transdermal administration was quite longer ($27.697 \pm 4.937 \text{ hr}$) compared to oral administration ($7.344 \pm 1.121 \text{ hr}$) (Table.4). The difference in C_{max} , $t_{1/2}$, AUC and MRT values following oral and transdermal administration was found to be statistically significant ($p < 0.05$).

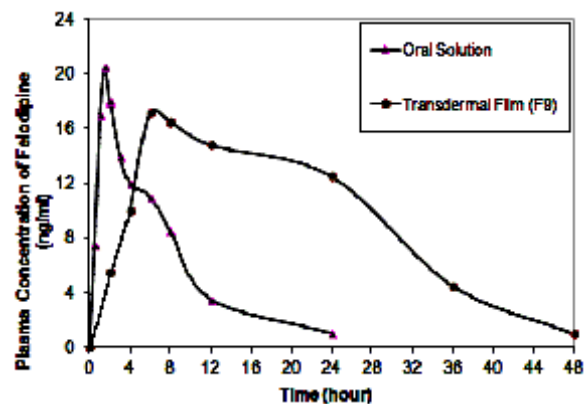


Fig. 8: Plasma concentration level of felodipine after oral and transdermal administration

Table 4: Pharmacokinetic parameters of felodipine after oral and transdermal administration

Pharmacokinetic parameters	Oral Solution	Transdermal Film : F9
C_{max} ($\mu\text{g}/\text{L}$)	20.5 ± 1.893	17.33 ± 1.887
t_{max} (hr)	1.5	6.33
AUC_{0-1} ($\mu\text{g}\cdot\text{hr}/\text{L}$)	146.845 ± 15.240	504.378 ± 81.402
AUMC_{0-1} ($\mu\text{g}\cdot\text{hr}^2/\text{L}$)	1078.179 ± 271.307	13969.943 ± 4649.003
MRT (hr)	7.344 ± 1.121	27.697 ± 4.937
$t_{1/2}$ (hr)	4.279 ± 0.998	16.762 ± 3.313

The summary of the *in vivo* performance of felodipine after oral and transdermal administration revealed a four time increase in the bioavailability after transdermal administration compared to oral route. The low oral bioavailability of FD is due to its extensive hepatic

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metabolism^{1,2}. The significant increase in bioavailability following transdermal administration indicated avoidance of a substantial amount of hepatic first pass metabolism associated with oral administration in rabbits and it is most likely due to the fact that the vascular system of the skin predominantly drains in to the superior venacava, thereby avoiding the initial first pass through the liver²³.

CONCLUSION

The fabricated transdermal film-F9 with ERL:HPMC (4:1) with 7.5% w/w PEG 400 as plasticizer and 4% w/w span 60 as permeation enhancer 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 *in vitro*, *ex vivo* and *in vivo* results of the study show the feasibility of designing and fabricating the rate controlled transdermal drug delivery system of felodipine in order to achieve improved bioavailability. 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 formulation. Further, these findings may help the industry to scale up for commercial production.

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