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SYSTEM DESIGN AND CHARECTERIZATION OF TRANDERMAL FILMS OF FELODIPINE

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ABSTRACT

The present investigation was taken up to prepare and evaluate a transdermal drug delivery system of felodipine to increase its bioavailability. The matrix type patches were prepared using the polymer blend of eudragit RL 100 (ERL)/RS 100 (ERS) by solvent 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 (PEG400) and glycerin were used as plasticizer and permeation enhancer, respectively. Incorporation of PEG 400 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 glycerin produced significant increase in the flux and permeability constant. The formulation with ERL : ERS ratio 4 : 1, 5% w/w glycerin as permeation enhancer and 10% w/w PEG 400 as plasticizer showed the best results, which exhibited the cumulative percentage of drug release of 63.57% and the cumulative amount of drug permeation across skin of 3557.2 μg/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 excipient. 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.

Key words: Transdermal therapeutic system, Felodipine, Eudragit, Glycerin, Skin permeation.

INTRODUCTION

Transdermal drug delivery systems (TDDS), also known as "patches" are discrete dosage forms designed to deliver a therapeutically effective amount of drug across the patient's skin in a controlled manner for a prolonged period of time. The first transdermal system "Transderm-SCOP" was approved by FDA in 1979 for the prevention of nausea and

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vomiting associated with travel particularly by sea. Currently, transdermal dug delivery is one of the most promising methods for drug application. 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].

Increasing number of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin. 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 arena[3]. Felodipine (FD), a potent calcium channel blocker, which is widely used in the treatment of hypertension and angina pectoris. Although it is rapidly and almost completely absorbed from the GIT, it undergoes extensive first pass metabolism resulting in a bioavailability of about 15% after its oral administration. Hence to achieve therapeutic concentration, frequent dosing or large doses are required. Oral administration of large dose of FD can produce nausea and other gastro-intestinal disturbances[4, 5]. Moreover, FD is an ideal candidate for the transdermal delivery because of their low molecular weight (384.3D), low dose (5-10 mg/day) and low melting point (142-145°C) and is having balanced hydrophilic-lipophilic characteristics (log P = 3.86)[6]. Hence to improve the bioavailability, therapeutic efficacy, patient compliance and to reduce the frequency of dosing and its side effects, transdermal drug delivery systems are better suitable for FD.

EXPERIMENTAL

Materials and methods

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. Polyethylene glycol 400 (PEG 400), glycerin, 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 cm^2 were fabricated for casting the patches.

(a) 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.

Table 1: Composition of formulations

F. Code	Polymer ratio ERL/ERS	ERL (mg)	ERS (mg)	FD (mg)	PEG 400 (mg)	Glycerin (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	35	-	7
F6	4 : 1	560	140	210	70	-	7
F7	4 : 1	560	140	210	35	35	7
F8	4 : 1	560	140	210	35	70	7
F9	4 : 1	560	140	210	70	35	7
F10	4 : 1	560	140	210	70	70	7

(b) Preparation of transdermal patches: Casting solution (5 mL) 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 cm^2). These patches were kept in desiccator for 2 days for further drying and wrapped in aluminium foil, packed in self-sealing covers[7-9].

Physico-mechanical characterization of transdermal patches

(a) Physical appearance: All the formulated transdermal patches were visually inspected for colour, flexibility, homogeneity and smoothness[10].

(b) 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 films[10-12].

(c) Weight uniformity: The films of different batches were dried at 60^{o}C for 4 hrs before testing. Five patches from each batch having diameter of 1 cm^{2} were weighed on a digital balance. The average weight and the standard deviation values were calculated from the individual weights[12].

(d) Folding endurance: Folding endurance was measured manually for the prepared films. A strip of film (2 cm x 2 cm) 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].

(e) 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 (Fig. 1) was used to carry out the measurement. 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 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).

(f) Hardness: The apparatus employed for hardness determination was designed in the laboratory using the literature report (Fig. 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 o 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 recorded[14,15].

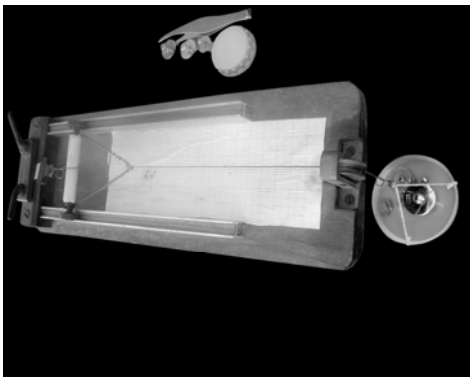

Fig. 1: Instrument for the measurement of tensile strength of films

Fig. 2: Instrument for the measurement of hardness of films

(g) Drug content uniformity: The film of 1 cm^2 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 determined[13].

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 cm^2 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 100 rpm 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 media[16-18].

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 cadaver 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. The experimental set up and procedure was same as conducted for in vitro study[18-20].

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; Kr = Ke.Cd.Vd.BW where, Kr is rate constant for drug release, Ke is the first order rate constant for drug elimination, Cd is the therapeutic drug concentration, Vd is the volume of distribution and BW is the standard body weight. For felodipine, $t_{1/2}$ = 12 h, Cd = 6.24 µg/L and Vd = 10 l and therefore the desired drug release rate can be calculated as Kr = (0.693/12) x 6.24 x 10 x 70 = 252.25 µg/hr. Hence, area of patch (A) required for desired release rate is A = Kr/ (Kp/S), where Kr is the required drug release rate (mg/h) and S is the surface area of the film subjected to diffusion (cm^2)[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 ± 0.5°C and 75 ± 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 charecteristics[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, placebo patch 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 (Fig. 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 (Fig. 4). The transdermal patch of 1 cm 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 l0 hrs. The patch was covered with silicone coated release liner[18].

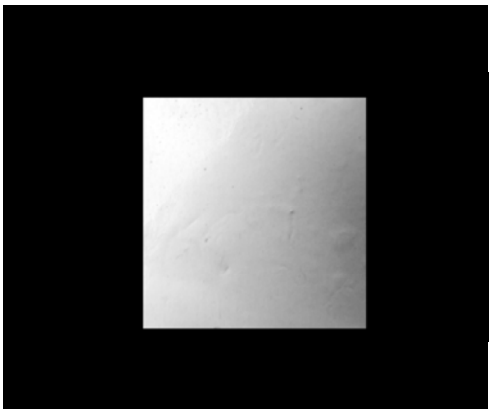

Fig. 3: Prepared transdermal film

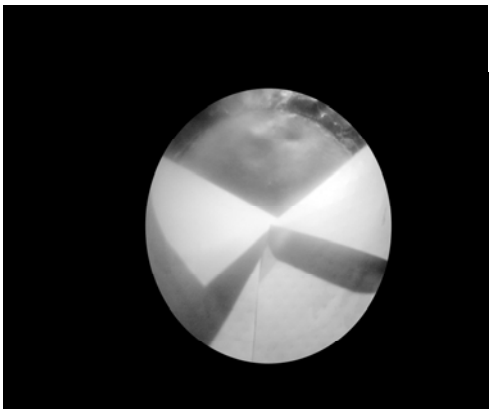

Fig. 4: Laminated transdermal patch

RESULTS AND DISCUSSION

Physico-mechanical characterization

In the present study, total ten patches were formulated for the optimization of 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 physicomechanical valuation data of the films was presented in Table 2.

Table 2: Physico-mechanical characters of formulated transdermal films

F. 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	70-80	6.8 ± 1.541	0.349 ± 0.066	0.438 ± 0.047
F2	0.213 ± 0.025	27.232 ± 0.208	90-100	8.2 ± 1.164	0.362 ± 0.073	0.423 ± 0.032
F3	0.206 ± 0.031	27.784 ± 0.177	110-120	8.7 ± 1.275	0.375 ± 0.051	0.396 ± 0.065
F4	0.214 ± 0.022	28.323 ± 0.251	120-130	9.5 ± 1.845	0.389 ± 0.012	0.387 ± 0.071
F5	0.218 ± 0.025	30.229 ± 0.527	140-150	13.3 ± 2.075	0.432 ± 0.062	0.372 ± 0.0240
F6	0.223 ± 0.032	30.943 ± 0.548	160-180	18.4 ± 2.204	0.471 ± 0.056	0.359 ± 0.048
F7	0.232 ± 0.035	32.370 ± 0.886	160-180	16.8 ± 2.081	0.458 ± 0.075	0.361 ± 0.068
F8	0.241 ± 0.043	33.637 ± 0.727	180-190	21.6 ± 1.947	0.507 ± 0.0530	0.352 ± 0.087
F9	0.236 ± 0.039	32.893 ± 0.648	200-220	24.3 ± 2.516	0.526 ± 0.057	0.347 ± 0.057

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. With respect to the physicochemical properties the formulation F4 was selected for further modification. Toenhance the flexibility and permeability, PEG 400 and glycerin were incorporated to F4 at 5%w/w, and 10% w/w concentrations in respect to the dry weight of the polymer. The plasticizer can diffuse in to and softens the polymer matrix. Folding endurance value were 70-80 for formulation F1 and 200-220 for formulation F9, other formulations were within these ranges, which shown that the presence of plasticizers 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 F10 film with 10%w/w of PEG 400 and 10%w/w of glycerin was not satisfactory because of its high hygroscopic, soft and sticky nature and it was excluded from further evaluation.

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 PEG 400 and glycerin. 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 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), PEG 400 and glycerin were increased the tensile strength and the percentage elongation where as the hardness of the film decreased.

Good uniformity of the drug content among the patches was observed for all the formulations which ranged from 95.278% to 99.166% (Table 3). Based on the initial drug loading, all the formulations were containing above 5.716 ± 0.0349 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 (1 cm^2) (mg) AM ± SD	Percentage of drug (1 cm^2) AM ± 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 ± 0.0266	95.556 ± 0.4433
F5	5.851 ± 0.0515	96.312 ± 0.3769
F6	5.773 ± 0.0536	98.043 ± 0.5587
F7	5.640 ± 0.0217	99.166 ± 0.4493
F8	5.691 ± 0.0381	95.890 ± 0.8706
F9	5.628 ± 0.0387	97.552 ± 0.5398

In-vitro drug release studies

In vitro drug release studies carried out to indicate the influence of polymer and plasticizers concentration on the release of the drug. The rate and amount drug released over 24 hrs were determined and results are summarized Figs. 5 and 6.

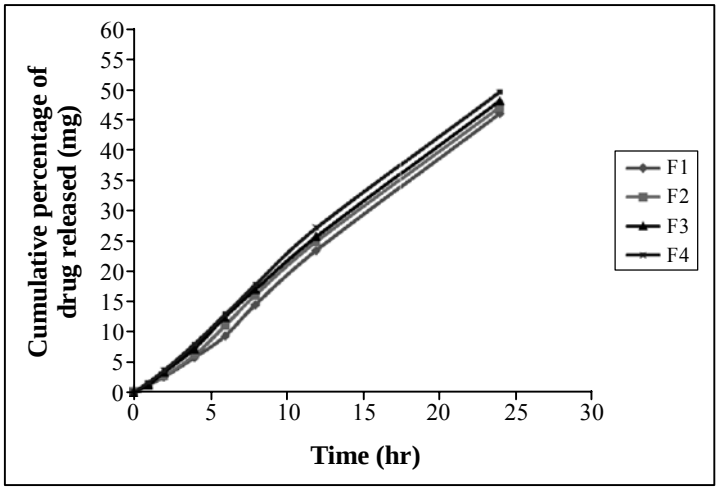

Fig. 5: Effect of polymer composition (ERL/ERS) on the *in-vitro* drug release of formulated transdermal films (F1 to F4)

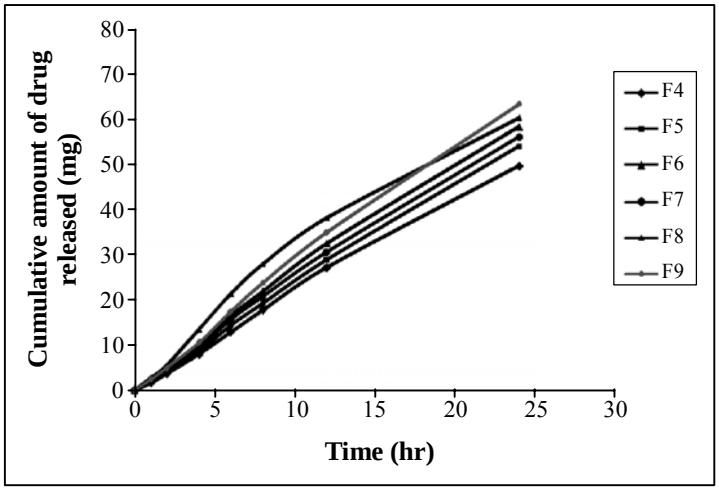

Fig. 6: Effect of the concentration of PEG 400 and glycerin on the *in vitro* drug release (F4 to F9)

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 FD was found to be enhanced significantly when plasticizers are incorporated to the formulation, it is indicated that the drug release rate increased gradually as the amount of plasticizer was increased. The films F9 exhibited greatest percentage of drug release (63.57%).

Data of *in vitro* release was fit into different kinetic equations to explain the release kinetics of FD. The kinetic models used were zero order equation, first order equation, Higuchi and Korsemayer-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 = 0.83 to 0.85) and first order (r^2 = 0.24 to 0.27) (Fig. 7). The results also suggest that, the concentration of glycerin and PEG 400 had major influence on drug release and 5% w/w glycerin and 10% w/w PEG 400 are most favorable concentration for constant and uniform release of FD from eudragit films.

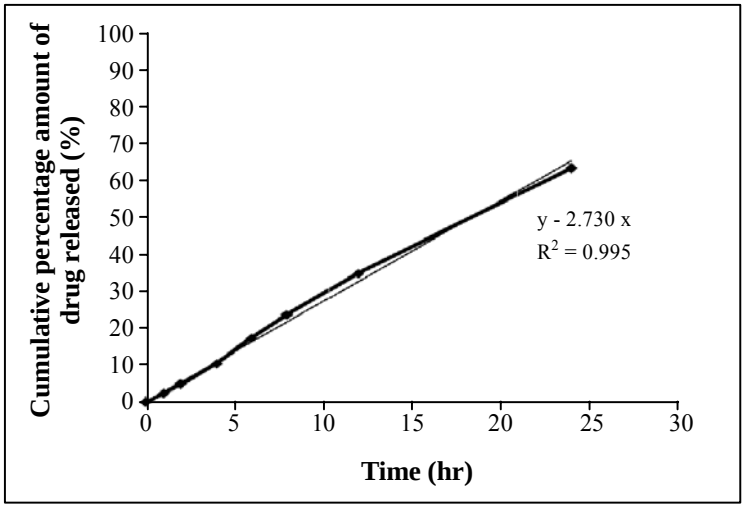

Fig. 7: Zero order release of felodipine from transdermal film-F9

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 glycerin can significantly improve the drug permeation characteristics through human cadaver skin (Fig. 8 and 9).

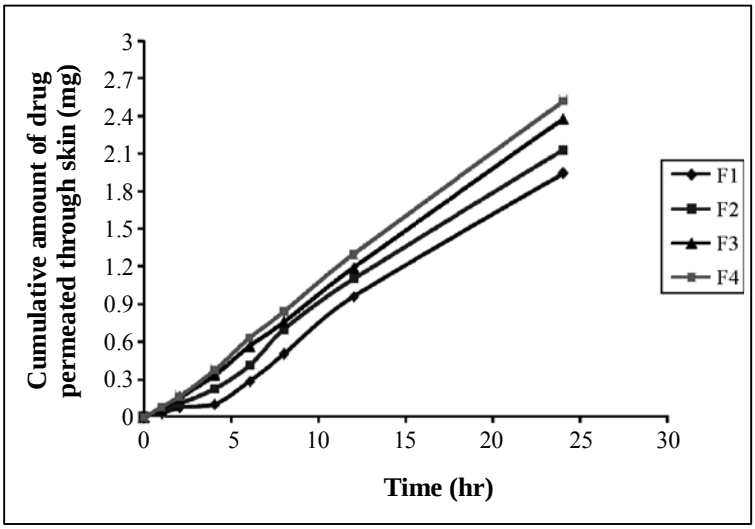

Fig. 8: Effect of polymer composition (ERL/ERS) on the *ex-vivo* skin permeation of drug from transdermal films (F1 to F4)

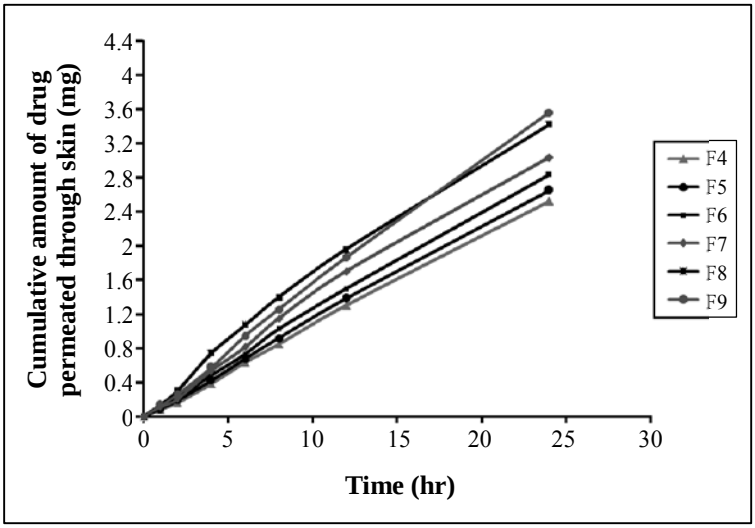

Fig. 9: Effect of the concentration of PEG400 and glycerin on the *ex-vivo* skin permeation of drug from transdermal films (F4 to F9)

Incorporation of glycerin 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 penetration (Fig. 10).

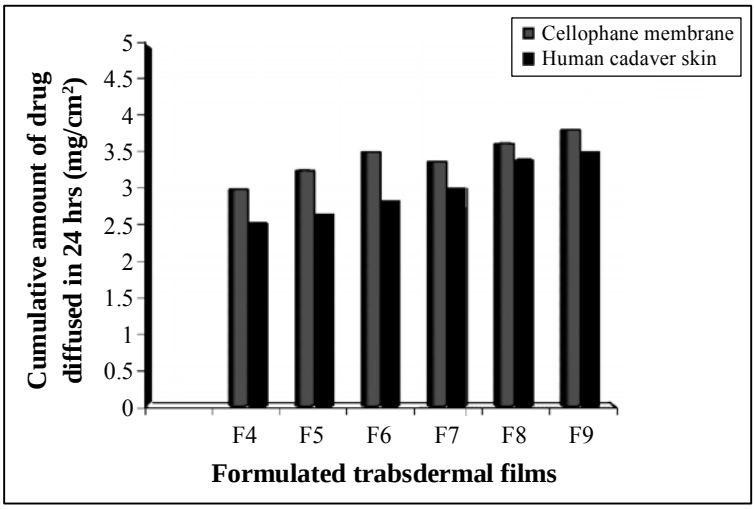

Fig. 10: Comparison of drug release and skin permeation from formulated transdermal films (F4-F9)

The *in vitro* drug release and ex *vivo* skin permeation studies revealed that the combined use of PEG 400 and glycerin increased the release rate and amount of the drug from the patches compared to that of their single use. The incorporation of PEG 400 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 glycerin into the films may be useful for attaining required drug permeation through skin. Thus, the film-F9 with ERL : ERS ratio 4 : 1, 5% w/w glycerin as permeation enhancer and 10% w/w PEG 400 as plasticizer showed the best results, which exhibited the cumulative percentage of drug release of 63.57% and the cumulative amount of drug permeation across skin of 3557 µg/cm^2 in 24 hrs. The transdermal flux, permeability coefficient and area of the film required for desired release rate for the transdermal film-F8 were calculated and are reported in Table 4.

Compatibility studies

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, indicating that there is no interaction between drug and polymers.

Stability study

Stability studies were carried out for 3 months and the films was 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. Drug release and permeation characteristics did not alter significantly during the stability testing period.

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	63.57 %
Cumulative amount of drug permeated through skin - 24 hr	3557.2 μg/cm^2
Lag time	1.8 hr
Transdermal flux	148.22 μg/hr/cm^2
Permeability coefficient	2.73 x 10^{-2} cm^2/hr
Targeted flux	252.25 μg/hr
Area of film required for TDDS	1.702 cm^2

Primary skin irritancy studies

Results of skin irritancy study revealed that neither blank patch nor patch containing FD showed negligible erythema or oedema on rabbit skin throughout the period of 48 hrs, indicating that FD and these polymeric films were compatible with the skin and hence can be used for transdermal application.

CONCLUSION

The choice of appropriate polymer blend and concentration of plasicizer and permeation enhancer are critical issues in matrix type transdermal drug delivery system. Based on the physico-mechanical, drug release and skin permeation characteristics, the present study conclude that, ERL 100/RS 100 (4 : 1) films with PEG 400 (10% w/w) and glycerin (5% w/w) are suitable to design matrix dispersion type transdermal films for FD. The fabricated transdermal delivery system containing FD 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. The findings of this result revealed that the poor bioavailability and gastric side effects on oral administration can be overcome by applying felodipine topically in the form of transdermal patch.

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