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Research paper

# Eudragits: Role as crystallization inhibitors in drug-in-adhesive transdermal systems of estradiol

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**Abstract**

A transdermal steroidal delivery system usually contains a high concentration of drug to obtain high drug fluxes. The present investigation involved the development of drug-in-adhesive transdermal systems of estradiol using synthesized acrylate copolymer (EA) of 2-ethylhexyl acrylate and acrylic acid. The effect of several variables such as varying drug polymer ratios, effect of Eudragit® RL PO and Eudragit® E PO and effect of drying temperatures on prevention of drug crystallization in the formulation matrix was investigated. The systems free from drug crystals were evaluated and compared with a marketed formulation with respect to its skin permeation profile. The optimized formulation was also subjected to accelerated stability testing. Eudragit® RL PO and Eudragit® E PO were found to be effective as crystallization inhibitors in the transdermal matrix systems tested. Formulations fabricated with Eudragit® E PO gave transparent systems with good film properties and a higher skin permeation profile as compared to that of the marketed system. Higher temperature and humidity conditions facilitated the formation of drug crystals, whereas no crystals were observed in the formulation matrix at 23 ± 0.5°C and at 30 ± 1°C for the period of 6 months studied. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords*: Estradiol; Transdermal; Eudragits; Acrylates; Crystallization inhibitors; Supersaturation; Permeation

## 1. Introduction

The efficacy of estrogen replacement therapy is well established both in the treatment of menopausal symptoms [1] and protection against long-term consequences of estrogen deficiency (osteoporosis and cardiovascular disease) [2]. In terms of tolerability, the natural hormone 17β-estradiol is the first choice for post-menopausal estrogen therapy. The transdermal administration of 17β-estradiol is clinically effective and has numerous advantages over the oral route [3]. In addition, the transdermal route is non-invasive, easy-to-use and well-accepted by the patients [3].

Numerous approaches have been investigated to enhance the rate of skin permeation. These include the use of different types of devices [4], incorporation of enhancers [5] or increased drug loading [6]. It has been demonstrated that the drug permeation increases with drug thermodynamic activity beyond saturation to a supersaturated level [7]. Thus, transdermal delivery systems (TDS) generally contain a high concentration of drug to promote high drug fluxes. However, these systems are thermodynamically unstable. As a consequence, the drug, which is readily dissolved during the manufacturing process and immediately thereafter, might partially re-crystallize during storage of these systems [8]. Such physical instability might lead to reduced drug fluxes over a period of storage. Therefore, prevention of drug crystallization becomes imperative to maintain the efficiency and quality of transdermal systems. One basic approach to enhancing the solubility of the drug in the patch formulation is prodrug formation [9]; other options for increasing the drug loading level in patches are adhesive modification [10], use of co-solvents and the use of crystallization inhibitors [11] within the supersaturated transdermal system.

Drug-in-adhesive systems are the recent second-generation systems wherein the drug is directly dispersed in the pressure sensitive adhesive itself. The saturation solubility for several sex steroids in standard pressure sensitive adhesives is low [8], hence there is a greater tendency for the drug to precipitate. This research endeavour was directed towards the prevention of drug crystallization in drug-in-adhesive transdermal systems of estradiol. The effect of

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formulation and process variables in the prevention of crystallization was assessed. Also, the efficacy of crystallization inhibitors was studied at accelerated stability conditions.

## 2. Materials and methods

### 2.1. Materials

Estradiol (ESD) was received as a gift sample from Cipla Ltd. (India). Backing membrane (Scotchpak # 1006) and release liner (Scotchpak # 1022) were generously gifted by 3M Pharmaceuticals (St. Paul, MN, USA). The acrylate copolymeric pressure sensitive adhesive (EA) of 2-ethylhexyl acrylate and acrylic acid was synthesized in our laboratory. Eudragit® RL PO and Eudragit® E PO were obtained as gift samples from Rohm GmbH (Germany). All chemicals and reagents employed were of analytical grade and were purchased from Ranbaxy Chemicals Ltd., India.

### 2.2. Design of drug-in-adhesive transdermal systems

Transdermal systems were fabricated by the solvent evaporation technique. A defined weight of the adhesive polymer (EA) was dissolved in ethyl acetate and the dry weight of this polymeric solution was determined. The volume of solution required to get a specified amount of polymer per patch was computed. The drug and other excipients were added, mixed uniformly and then cast on a backing membrane. The patches were dried, covered with a release liner and then smoothened by rolling with a 45-pound roller with no additional pressure. The finished patches were kept in a dessicator before use.

### 2.3. Formulation optimization

A series of formulations were tried and the preparative procedure was optimized with respect to formulation and process variables. The effect of various drug-polymer ratios - 1:1, 1:2.5, 1:5, 1:10, 1:15 and 1:20 on drug crystallization was investigated. The effect of Eudragit® RL PO (E-RL PO) and Eudragit® E PO (E-E PO) in a concentration range of 0.25–2 mg/cm$^2$ on prevention of crystallization in transdermal matrix was also evaluated. In addition, the patches fabricated were subjected to three different drying conditions viz. 55 ± 0.5°C, room temperature (30 ± 1°C) and 23 ± 0.5°C and its effect on the formation of drug crystals was studied.

### 2.4. Drug-excipient interaction studies

These were performed on formulation EA-E PO2 (ESD-EA in a drug polymer ratio of 1:20 containing E-E PO 2 mg/cm$^2$), which was free of drug crystallization. The studies included infra-red spectroscopy (Jasco FT/IR 5300 spectrophotometer, by the KBr disc method) and differential scanning calorimetry (Mettler TA 4000 thermal analyzer, heating rate of 10°C/min over a temperature range of −100 to +250°C). The spectra/thermogram of the formulation was recorded and compared with that of the drug and individual excipients for any significant changes.

X-ray diffraction studies (X-ray Diffractometer model: Seimens 5000, Nickel filtered $CuK_{\alpha 1}$ radiation having a wavelength of 1.5106 Å, operating at 35 kW and 20 mA in the range ($2\theta$) of 5–70° at a scanning rate of 2°/min) were also performed to determine the state in which the drug existed in the transdermal matrix.

### 2.5. Evaluation of developed TDS

The systems free of drug crystallization were evaluated for weight and thickness uniformity, drug content and content uniformity, peel strength, in-vitro release and skin permeation kinetics. For study of each of these evaluation parameters, six systems were considered ($n = 6$). The peel strength of the developed TDS was determined using a 180° peel strength tester (Khushboo Pvt. Ltd., India). The drug-in-adhesive coated backing membrane (4 cm$^2$) was fixed on a stainless steel plate. The tape was then pulled from the substrate (human skin/release liner) at 180° angle at a fixed rate of 300 mm/min by means of a hook attached to a spring balance. The point at which detachment begins to occur was taken as the peel strength expressed in g/4 cm$^2$. The peel strength on human skin was determined using six healthy human volunteers. The in-vitro release pattern was studied using Keshary–Chien type diffusion cells having a volume of 10 ml and effective area of 1 cm$^2$. A patch of 1 cm$^2$ was applied, with 40% v/v PEG 400 as the diffusion medium and temperature being maintained at 37 ± 0.5°C. Aliquots (3 ml) were withdrawn at 0.5, 1, 1.5, 2, 3, 5, 7, 9 and 12 h intervals and were replaced with fresh medium. Skin permeation studies involved mounting the whole excised abdominal guinea pig skin (epidermis and dermis) on a modified Keshary–Chien type diffusion cell of 4.5 ml capacity. The dermal side was kept continuously in contact with receptor medium, which consisted of 40% v/v PEG 400 solution [12,13]. Samples (0.5 ml) were withdrawn over a period of 1, 2, 3 and 4 days and replaced with fresh medium. The concentration of drug for in-vitro release and skin permeation studies was determined by HPLC (Jasco PU-980 intelligent HPLC pump equipped with a Jasco UV-975 UV/VIS intelligent detector). The permeation profile was compared with a marketed transdermal system. Diffusion coefficient, permeability coefficient and partition coefficient were determined using the equation described by Higuchi [14].

The optimized systems having skin permeation kinetics similar/better than the marketed system were also evaluated for wear performance, moisture content (Karl–Fischer method on a Karl–Fischer Autotitrator, Veego-Matic D), residual ethyl acetate content and skin irritation. The wear performance test [15] was conducted utilizing a panel of 10 human subjects. The patch was applied to the upper arm and

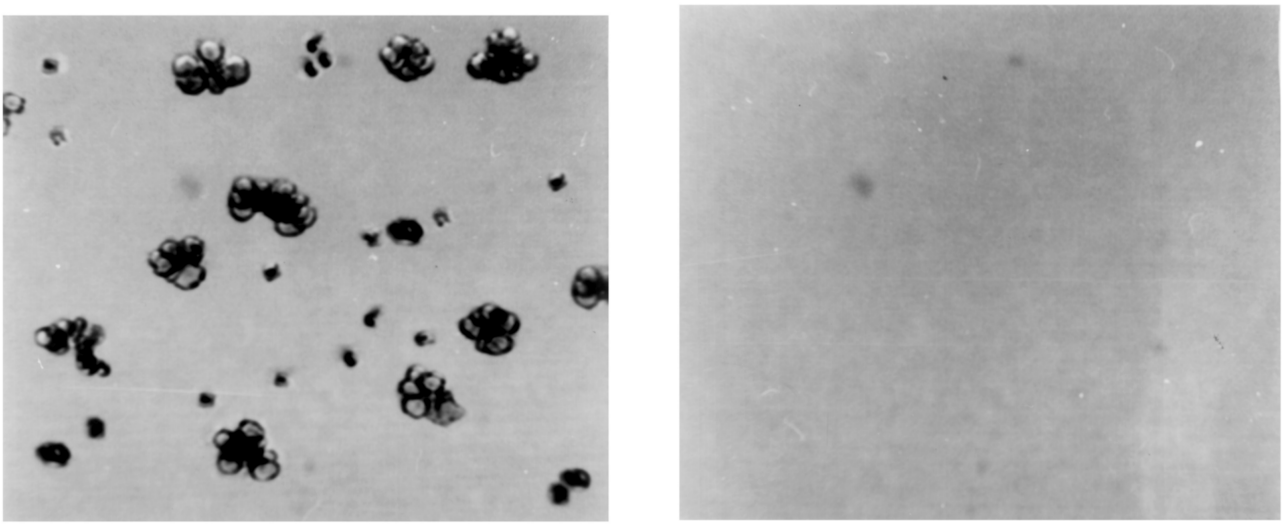


Fig. 1. Microscopic images I and II showing the inhibition of drug crystallization on addition of E-E PO (1.5 or 2 mg/cm$^2$) in ESD-EA system. Image (I): ESD-EA system (drug polymer ratio of 1:20); Image (II): EA-E PO2 (ESD-EA in a drug polymer ratio of 1:20 containing E-E PO 2 mg/cm$^2$).

subjects were allowed to engage in normal activities. At the end of 96 h, adhesion to the skin and adhesive transfer on removal was evaluated. Adhesion was rated from 0 (tape off) to 7 (perfect adhesion). Adhesive transfer was rated from 0 (no residue) to 2 (heavy residue). The residual ethyl acetate content was determined by head-space gas chromatography (GC 8000 Top with headspace autosampler). The column employed was a HP-624 [(6%) cyanopropyl-phenyl-(94%)-dimethylsiloxane copolymer] with a oven temperature of 40°C. The injection port temperature was fixed at 140°C. A flame ionization detector at a temperature of 260°C was used and the carrier gas employed was nitrogen at a flow rate of 3.5 ml/min. The skin irritation potential of the developed TTS was evaluated by performing the Draize test [16].

### *2.6. Stability studies*

The optimum formulation (EA-E PO2, patch size: 4 cm$^2$) was packed in polythene lined aluminium foils, 4 mils in thickness and subjected to accelerated temperature and humidity conditions as per the ICH guidelines [17] viz. 40°C/75%RH and 30°C/60%RH. In addition, patches were kept at room temperature (30 ± 1°C) and 23 ± 0.5°C. Samples were withdrawn at predetermined time intervals of 7, 15, 30, 45, 60, 90 and 180 days. Appearance of crystals was monitored visually and microscopically on a microscope with a built-in image processing system (Image-Pro Plus™, Version 1.0) wherein the images could be transformed to a pictorial form. The samples were also evaluated for any changes in weight and thickness uniformity, drug content and content uniformity, peel strength, moisture content, in-vitro release and skin permeation kinetics.

## 3. Results and discussion

In the systems containing only the drug and the polymer (ESD-EA systems), an increase in the polymer concentration from 1:1 to 1:20 resulted in a decrease in the drug crystallization. However, no complete inhibition of crystallization was observed as seen in Fig. 1, microscopic image (I). A drug-polymer ratio of 1:20 was selected for further studies.

Incorporation of E-RL PO in ESD-EA (1:20) systems could effectively prevent drug crystallization. No drug crystallization was observed in systems containing 0.5, 1.0, 1.5 and 2.0 mg/cm$^2$ of E-RL PO. However, these systems were found to be opaque and opacity increased with increase in the E-RL PO concentration. At concentrations of 1.5 and 2 mg/cm$^2$ of E-RL PO, the films obtained were highly opaque, displayed non-uniformity, showed the presence of wrinkles and exhibited poor adhesive transfer (mean score of 2 ± 0.0). Placebo films of E-RL PO in EA system (without drug) also gave opaque non-uniform films as compared to the transparent placebo films fabricated with only EA. Hence, the opacity could be attributed as a characteristic of E-RL PO itself. The drying temperatures did not have any significant effect on the property or adhesive nature of the film.

In the case of ESD-EA (1:20) systems wherein E-E PO was tried as a solubiliser, increase in concentration from 0.25 to 1 mg/cm$^2$ decreased the extent of drug crystallization. At concentrations of 1.5 mg/cm$^2$ (designated as EA-E PO1.5) and 2 mg/cm$^2$ (EA-E PO2) no crystallization was observed as depicted in Fig. 1, microscopic image (II). The developed systems were transparent unlike the patches fabricated with E-RL PO. The prevention of crystallization could be attributed to the weak association of the proton of

the quaternary amine of E-RL PO/ E-E PO with the hydroxyl group of the drug. This could either bring about solubilisation of the drug or prevent collision of drug molecules and subsequent formation of nuclei. The polymer (E-RL PO/ E-E PO) could also get adsorbed on the drug molecule, thus forming a protective coat on the surface resulting in stabilization. It was observed that there was no significant difference in the nature and the adhesive character of the film at drying temperatures of 23°C and room temperature (30°C). However at 55°C, the films were found to be slightly wrinkled due to rapid drying. Hence, 23°C was selected as the drying temperature.

A comparison of the infrared spectrum of the formulation matrix with the IR spectra of its individual components was done to observe any spectral shifts in the matrix. The infrared spectra of the drug, EA copolymer, E-E PO and the formulation matrix (EA-E PO2) are depicted in Fig. 2. The group assignments are as discussed in Table 1. The infrared spectra of the optimized formulation EA-E PO2 revealed all the peaks of the adhesive copolymer. The characteristic acrylate ester peak of the adhesive was observed at 1736 $cm^{-1}$. Some characteristic peaks corresponding to the drug were found to be overlapping in the region as that of the polymer. No significant shifts in the peaks corresponding to the drug or the adhesive polymer were observed in the formulation matrix. In the DSC studies, the DSC thermogram for the drug gave a sharp endotherm at 178°C. The adhesive polymer (EA) did not exhibit any characteristic peak. E-E PO showed a characteristic Tg at 46°C. In the case of the formulation matrix EA-E PO2, no peak of the drug was observed, suggesting that the drug was evenly solubilised in the matrix. The comparative DSC thermograms of the drug, adhesive polymer, E-E PO and formulation matrix (EA-E PO2) are depicted in Fig. 3.

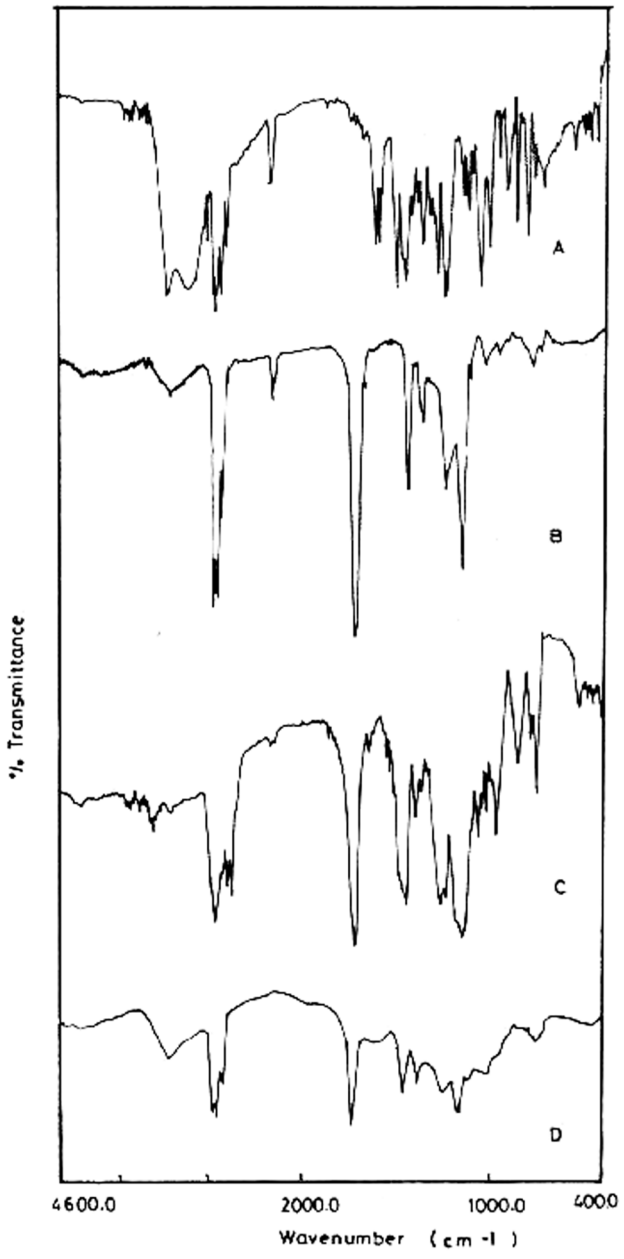


Fig. 2. Infrared absorption spectra. (A) Estradiol. (B) EA. (C) E-E PO. (D) EA-E PO2.

X-ray diffraction study was performed for the drug, the adhesive polymer (EA) and the optimized formulation free of drug crystals, EA-E PO2. Estradiol (pure drug) existed in its crystalline state and this was clearly depicted in its XRD pattern, which showed the presence of sharp peaks. In the case of the adhesive polymer, the diffraction pattern was in general amorphous in nature. A few peaks were observed between 20–30° ($\theta$). This could be due to the low degree of crystallinity [18]. The XRD pattern of the formulation matrix EA-E PO2, was similar to that of the adhesive polymer itself. No sharp peaks corresponding to the drug was observed. This suggests that the drug could be existing in an amorphous/solubilised state in the formulation matrix. The comparative XRD patterns of the drug, adhesive polymer (EA) and the formulation EA-E PO2 are depicted in Fig. 4.

The systems free from drug crystallization EA-E PO1.5 and EA-E PO2 were considered for evaluation. Microscopic evaluation of formulations EA-E PO1.5 and EA-E PO2 did not reveal the presence of any crystals. The developed patches complied with the tests for weight and thickness uniformity, drug content and content uniformity with a RSD of less than 2%. The weight of the patches was found to be in the range of 11–11.6 mg, thickness of 120–125 μm and drug content values within the range of 99–100.50% w/w.

Addition of E-E PO did not alter the adhesive character of the adhesive polymer, hence no change in the peel strength values was observed even with an increase in E-E PO concentrations. In the case of both the formulations EA-E PO1.5 and EA-E PO2, the peel strength values was found to be 40.00 ± 2.59 and 40.00 ± 1.73 g/4 $cm^2$ respectively with respect to the release liner; 85.00 ± 5.78 and 85.00 ± 3.24 g/4 $cm^2$ respectively with respect to skin.

The data from the in-vitro study was fit into various kinetic models to determine the kinetics of drug release.

Table 1
Interaction studies: infrared spectroscopy

| Components | Wave number ($cm^{-1}$) | Group assignment |
|---|---|---|
| Estradiol | 3447 | O–H stretching |
| | 2961, 2936, 2862 | C–H stretching, alkane |
| | 1680 | C–C multiple bond stretching, alkene |
| | 1585 | C–C multiple bond stretching, aromatic |
| EA (adhesive polymer) | 3452 | O–H stretching |
| | 2961, 2932, 2862 | C–H stretching, alkane |
| | 1736 | C = O ester stretching |
| | 1462 | C–H bending, alkane, $–CH_2$ and $–CH_3$ |
| | 1381 | C–H bending, alkane, gem-dimethyl |
| E-E PO | 3435 | O–H stretching |
| | 2953 | C–H stretching, alkane |
| | 2822, 2772 | Dimethyl amino |
| | 1734 | C = O ester stretching |
| EA-E PO2 (EA + drug + E-E PO 2 $mg/cm^2$) | 3452 | O–H stretching |
| | 2959, 2928, 2858 | C–H stretching, alkane |
| | 1736 | C = O ester stretching |
| | 1460 | C–H bending, alkane, $–CH_2$ and $–CH_3$ |
| | 1383 | C–H bending, alkane, gem-dimethyl |

The coefficient of regression ($r$) for zero, first-order and Higuchi models were computed and are as listed in Table 2. The release from both the formulations EA-E PO1.5 and EA-E PO2 followed a Q Vs $t^{1/2}$ relationship ($r = 0.9981$ and $r = 0.9979$ respectively) with only 50–55% of the drug being released in a period of 12 h. The in-vitro release profiles for EA-E PO1.5 and EA-E PO2 systems are depicted in Fig. 5 (A).

Eudragit® E PO was found to have an enhancing effect on the permeation of estradiol. An increase in the permeation rate was observed with increasing concentration of E-E PO in the ESD-EA matrix. This is clearly apparent from the values of flux, diffusivity, permeability coefficient and vehicle/skin partition coefficient which was found to be 4.6190 $\mu g/cm^2$/day, $32 \times 10^{-5}$ $cm^2$/day, $10.16 \times 10^{-3}$ cm/day and 1.5882 respectively for EA-E PO2 system as compared to 3.1356 $\mu g/cm^2$/day, $14.30 \times 10^{-5}$ $cm^2$/day, $6.8980 \times 10^{-3}$ cm/day and 2.4130 respectively for the EA-E PO1.5 system. It is known that the stratum corneum serves as a rate limiting membrane for the process of permeation. In addition, the drug is present in high concentration. Hence, a zero order kinetic model for permeation was concluded. It was also suggested that application of these systems on the skin would result in moisture uptake to some extent. This would bring about a reduction in the solubility of estradiol, resulting in now supersaturated systems with increased thermodynamic activity. This would enhance the diffusivity of the drug molecules through the skin resulting in enhanced permeation. The comparative skin permeation profiles for EA-E PO1.5, EA-E PO2 and marketed TDS are depicted in Fig. 5 (B). The developed systems showed higher permeation as compared to the marketed TDS.

Wear performance test was performed only on the optimized formulations EA-E PO1.5 and EA-E PO2. The developed systems exhibited good adhesion with a mean score of $5.7 \pm 0.08$ and $5.9 \pm 0.05$ for EA-E PO1.5 and EA-E PO2 respectively. In addition, both the formulations exhibited excellent adhesive transfer on removal (mean score of $0 \pm 0.0$). The moisture content of the optimized formulations was found to be $0.65 \pm 0.04$ and $0.58 \pm 0.05$ for formulations EA-E PO1.5 and EA-E PO2 respectively. In the head-space gas chromatography experiments the retention time of ethyl acetate was found to be $4.27 \pm 0.02$ min. No peak of ethyl acetate was observed when the optimized transdermal systems EA-E PO2 was subjected to gas chromatography analysis. Thus, it can be concluded that the residual ethyl acetate content in the system was less than the detection limit of 1 ppm. The results of the skin irritation test carried out in healthy female rabbits ($n = 6$) reveal that both the formulations showed no signs of reddening (erythema) or oedema at the site of application during the period of study.

The patches were observed for drug crystallization regularly during the stability studies at various storage conditions. No crystallization was observed in the TDS matrix, during 6 months of storage at $23 \pm 0.5$°C and at room temperature. At 30°C/60%RH and 40°C/75%RH, crystallization was observed at 6 months and 5 months respectively. These observations suggest that temperature and humidity are critical factors governing the induction time of steroid crystallization in a solid matrix system. Storage temperatures may affect drug crystallization through other factors. For example, crystallization is controlled by diffusion of a drug molecule on to the drug crystals and diffusion in turn is dependent on temperature. Higher temperature could enhance diffusion rate of molecules resulting in crystal

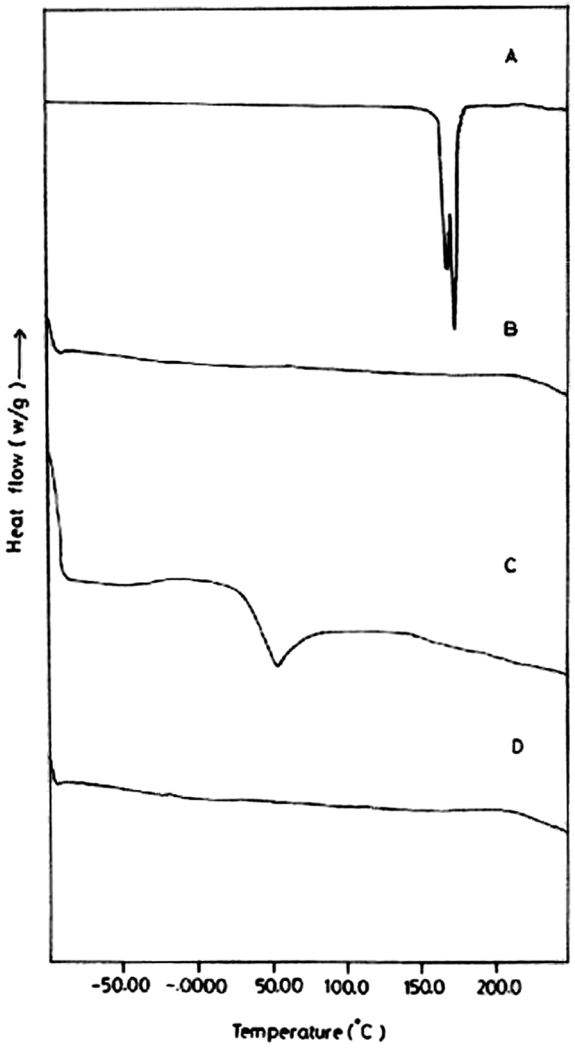


Fig. 3. Differential scanning calorimetric thermograms. (A) Estradiol. (B) EA. (C) E-E PO. (D) EA-E PO2.

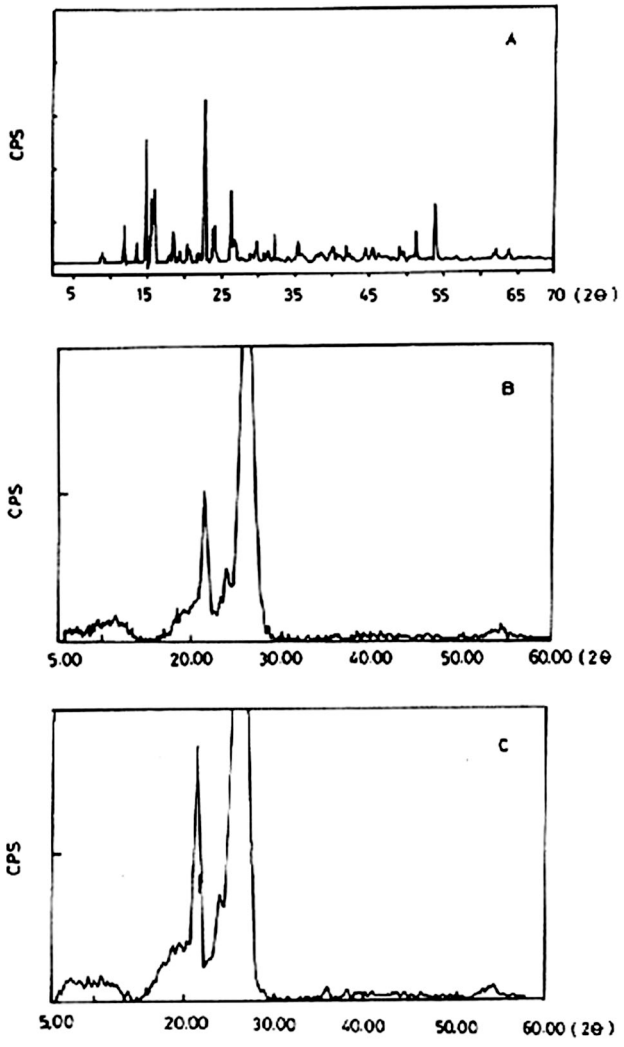


Fig. 4. X-ray diffractometric spectra. (A) Estradiol. (B) EA. (C) EA-E PO2.

Table 2
Fit of various kinetic models for ESD in EHA-AA system: effect of E-E PO as solubiliser ($n$ =6)[a]

| In-vitro release data | | | Skin permeation data | | |
|---|---|---|---|---|---|
| Parameters | EA-EPO1.5 | EA-EPO2 | Parameters | EA-EPO1.5 | EA-EPO2 |
| Zero order | | | Zero order | | |
| *r* | 0.9452 | 0.9511 | *r* | 0.9971 | 0.9948 |
| Rate | 4.0242 | 3.9051 | Rate | 0.6898 | 1.0162 |
| First order | | | First order | | |
| *r* | 0.9769 | 0.9777 | *r* | 0.9973 | 0.9949 |
| Rate | − 0.0266 | − 0.0250 | Rate | − 0.0030 | − 0.0045 |
| Higuchi | | | Higuchi | | |
| *r* | 0.9981 | 0.9979 | *r* | 0.9644 | 0.9768 |
| Rate | 15.8142 | 15.2492 | Rate | 1.3494 | 2.0187 |

[a] Rate, rate constant (day$^{-1}$); *r*, coefficient of regression.

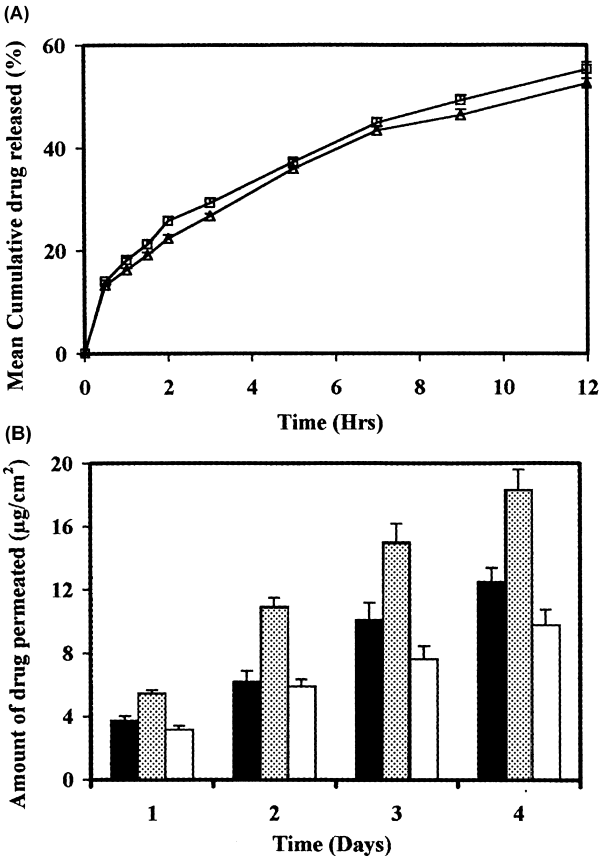


Fig. 5. (A) In vitro release of ESD from ESD-EA systems. Effect of E-E PO concentration. Data presented as mean ± SD ($n = 6$). (□) EA-E PO1.5; (△) EA-E PO2. (B) Skin permeation of ESD from ESD-EA systems. Effect of E-E PO concentration. Data presented as mean ± SD ($n = 6$). (■) EA-E PO1.5; (▥) EA-E PO2; (□) marketed.

formation. In addition, high humidity conditions could favour crystallization due to the low aqueous solubility of estradiol. Crystallization would then result in a decrease in skin permeation. The comparison of the permeation parameters for ESD in EA-E PO2 systems when subjected to stability evaluation at 40°C/75%RH is depicted in Table 3. It clearly indicates the decrease in the flux, diffusivity coefficient, permeability coefficient with a parallel increase in the vehicle/skin partition coefficient values due to crystallization. No significant changes in weight uniformity, thickness uniformity, drug content, content uniformity and peel strength were observed.

Table 3
Comparison of permeation parameters for ESD in EA-E PO2 systems during stability study at 40°C/75%RH ($n = 6$)[a]

| Parameters | 0 day | 15 day | 30 day | 60 day | 90 day | 180 day |
|---|---|---|---|---|---|---|
| Zero order | | | | | | |
| *r* | 0.9944 | 0.9945 | 0.9945 | 0.9974 | 0.9971 | 0.9973 |
| Rate | 1.0161 | 1.0087 | 1.0089 | 1.0270 | 0.9845 | 0.8378 |
| *J* | 4.6186 | 4.5850 | 4.5860 | 4.6680 | 4.4750 | 3.8080 |
| $D \times 10^{-5}$ | 31.9904 | 31.4181 | 31.3098 | 31.9064 | 29.2412 | 21.0404 |
| *P* | 0.0102 | 0.0101 | 0.0101 | 0.0103 | 0.0098 | 0.0084 |
| *K*p | 1.5881 | 1.6053 | 1.6112 | 1.6094 | 1.6834 | 1.9909 |

[a] Rate, rate constant ($day^{-1}$); *r*, coefficient of regression; *J*, flux ($\mu g/cm^2$/day); *D*, diffusivity coefficient ($cm^2$/day); *P*, permeability coefficient (cm/day); *K*p, partition coefficient.

## 4. Conclusion

The optimized systems exhibited good adhesion and excellent adhesive transfer on removal, with no skin irritation potential. Eudragit®RL PO and Eudragit®E PO were found successful in preventing crystallization in drug-in-adhesive transdermal system of estradiol. An increase in the skin permeation rate was observed with increasing E-E PO concentration in the ESD-EA matrix. However, high temperature and humidity conditions during storage were found to facilitate the process of crystallization. Hence, selection of suitable solubilisers and storage conditions were found to be critical in the prevention of drug crystallization.

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