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ORIGINAL ARTICLE

Damar Batu as a novel matrix former for the transdermal drug delivery: in vitro evaluation

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Abstract

Purpose: Damar Batu (DB) is a novel film-forming biomaterial obtained from *Shorea* species, evaluated in this study for its potential application in transdermal drug delivery system. *Methods*: DB was characterized initially in terms of acid value, softening point, molecular weight (M_w), polydispersity index (M_w/M_n), and glass transition temperature (T_g). Neat, plasticized films of DB were investigated for mechanical properties. The biomaterial was further investigated as a matrix-forming agent for transdermal drug delivery system. Developed matrix-type transdermal patches were evaluated for thickness and weight uniformity, folding endurance, drug content, in vitro drug release study, and skin permeation study. *Results*: On the basis of in vitro drug release and in vitro skin permeation performance, formulation containing DB/Eudragit RL100 (60 : 40) was found to be better than other formulations and was selected as the optimized formulation. IR analysis of physical mixture of drug and polymer and thin layer chromatography study exhibited compatibility between drug and polymer. *Conclusion*: From the outcome of this study, it can be concluded that applying suitable adhesive layer and backing membrane-developed DB/ERL100, transdermal patches can be of potential therapeutic use.

Key words: *Diltiazem hydrochloride; in vitro permeation; in vitro release; matrix system; transdermal drug delivery*

Introduction

Skin, the largest organ of the human body, provides a painless and patient-friendly interface for systemic drug administration. In addition to providing a leading edge over injections and oral routes by increasing patient compliance and avoiding first pass metabolism, respectively, the transdermal route provides sustained and controlled delivery. It also allows continuous input of drugs with short biological half-lives and can eliminate pulsed entry into systemic circulation, which often causes undesirable side effects[1–4]. Technological discoveries, over the last decade, have proven the feasibility of using several methodologies for enhancing transdermal drug delivery[5]. With a diverse set of tools to enhance skin permeability, the future of transdermal drug delivery looks brighter. The challenge now lies in converting these discoveries into useful products, utilizing newer excipients and technologies[6].

Damar Batu (DB) is a kind of Gum Damar, but it is not taken directly from the tree. DB (Gum) comes out from hard wood tree and falls to the ground. It resembles a stone with black or dark brown color inside. It is a petrified natural resin of ancient shorean trees. Batu (stone) refers to the opaque, stone- or pebble-shaped Damar collected from the ground. It is much harder than other resins and yellowish to brown in color. They are obtained from *Shorea* species such as *Shorea lamellata* Foxw., *Shorea virescens* Parijs, *Shorea retinodes* Sloot., *Shorea guiso*, and *Shorea robusta*, Family *Dipterocarpaceae*[7]. DB contains about 40% α-resin, 22% β-resin, 23% dammarol acid, and 2.5% water. DB was mainly used as an emulsifier and stabilizer for the production of color, paints, inks, and aromatic emulsions in food and cosmetic industries and also in the manufacture of paper, wood, varnishes, lacquers, polishes, and additives for beverages[8]. It has also been

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tried as water-resistant coating in pharmaceutical and dental industries for its strong binding properties[9].

Diltiazem hydrochloride (DH) is a calcium channel blocker used in the treatment of arrhythmia, angina pectoris, and hypertension. Literature reveals that it undergoes variable and extensive first pass metabolism showing only 40% bioavailability on oral administration[10,11]. Although liver is considered to be the major organ of DH biotransformation, the extra hepatic organs such as intestine and lungs contribute to the first pass uptake and systemic elimination of DH. Transdermal administrations of drugs, which undergo first pass metabolism, can improve the bioavailability and reduce the dosing frequency compared with the oral route. DH has already been investigated for transdermal delivery[12–14]. In this research work, matrix-type transdermal patches were prepared with DB, alone and in combination with Eudragit RL100 (ERL100), using DH as a drug model. These patches were then evaluated for thickness and weight uniformity, folding endurance, drug content, in vitro drug release, in vitro skin permeation studies, and skin irritation studies.

Materials and methods

DB was purchased from Padmavati Enterprise (Mumbai, India); chloroform from SRL (Mumbai, India); DH obtained as a gift sample from Torrent Pharmaceutical Ltd. (Ahmadabad, India); Eudragit RL100 received as a gift sample from Rohm Pharma (Darmstadt, Germany); and dibutyl sebacate (DBS) from Morflex Inc. (Greensboro, NC, USA). Other chemicals used were of AR grade.

Polymer characterization

DB was purchased locally and characterized for various physicochemical properties, such as color, acid value, softening point, molecular weight, and glass transition temperature. Acid value was calculated using the following formula: acid value = $5.61n/w$, where n is the number of milliliters of 0.1 M potassium hydroxide required and w is the weight in grams of substance. Softening point is determined by Herculus drop technique. Molecular weight (M_w) and glass transition temperature (T_g) were determined using gel permeation chromatography and differential scanning calorimeter (DSC), respectively. Polymer samples for molecular weight determination were eluted though a PL Gel 3 µm mixed column at a flow rate of a 1.0 mL/min using tetrahydrofuran (THF) as a solvent using a gel permeation chromatography system equipped with a differential refractometer detector (La-Chom L-7490). For calibration purpose, polystyrene standards (Polysciences, Germany) were used. For the determination of the glass transition temperature, approximately 6 mg of sample was placed on the aluminum pan and scanned over a temperature range of 0–60°C at a rate of 5°C/min using DSC 7 (Perkin Elmer). Samples were scanned in triplicate.

Mechanical characterization of the DB films

Films of DB were prepared on the mercury substrate by solvent casting method[15], using 10% (w/v) solution in chloroform. To evaluate the plasticizer effect, plasticizer (DBS) was added in concentrations of 10%, 20%, and 30% (w/w) (based on total weight of the polymer) in solution. Casted films were dried at a room temperature for 24 hours. The casted films after drying were carefully cut into film strips (length 42 mm × width 20 mm) and investigated for the mechanical properties such as tensile strength and percent elongation[16] using Instron Instrument (Model 4467, Instron Corp., Canton, MA, USA). The method used for evaluating the mechanical properties was based on guidelines of the American Society for Testing Materials, method D 882-95a[17]. Measurements were made at a crosshead speed of 10 mm/min and gauge length of 50 mm at 50% relative humidity (RH) and 25°C temperature. For each film specimen, all the parameters were determined in triplicate.

Preparation of polymeric films of DH

Matrix-type films of DH composed of DB alone and DB with ERL100 in varying proportions were prepared using solvent evaporation technique on mercury substrate. Drug matrix was prepared by dissolving requisite amount of drug, DB, and ERL100 in chloroform. To this solution, DBS was added in required concentration as a plasticizer and the whole solution was sonicated for 5 minutes. All the formulations were developed using drug loading of 20% (w/w) (based on the dry weight of the polymer). The uniform solution obtained was then poured in a glass bangle of 6.2 cm diameter placed on the mercury surface and dried at room temperature for 24 hours. Controlled solvent evaporation was achieved by placing an inverted funnel over the Petri dish[14]. The films were removed after complete removal of the solvent and kept in the desiccator until used.

Physicochemical characterization of DH transdermal patches

Transdermal patches of 4.906 cm^2 were taken out from each casted film after complete drying and evaluated for the following physicochemical properties.

Thickness and weight uniformity

The thickness of the patch at three different points was determined using thickness gauge (Oswa Scientific, Ambala, India), and the patches were then weighed individually using digital balance (Ohaus Corp., Pine Brook, NJ, USA) to determine the weight of each patch taken out from the casted film.

Folding endurance test

Folding endurance test was carried out by folding the patch at the same point a number of times till it broke[18]. The test was carried out to check the efficiency of the plasticizer and the strength of the film prepared using varying ratios of the polymers. The test was carried out in triplicate.

Drug content uniformity

Films of specified area were cut and weighed accurately. Pieces were taken into a 100-mL volumetric flask containing double-distilled water, and the flask was sonicated for 8 hours. A blank was prepared in the same manner using a drug-free placebo patch of same dimensions. The solution was then filtered using a 0.45-μm filter and analyzed spectrophotometrically for DH content at 236 nm[19].

In vitro drug release studies

The paddle-over-disc method was employed for the assessment of the release of the drug from the prepared patches[20]. Dry films of 4.906 cm^2 area were cut, weighed, and fixed over a glass disc with an adhesive. The disc was then placed in 900 mL phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32 ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass disc and operated at a speed of 50 rpm. Samples (10 mL aliquots) were withdrawn at appropriate time intervals up to 24 hours and analyzed for drug content at 236 nm using Shimadzu double-beam UV-visible spectrophotometer. Fresh prewarmed buffer solution (10 mL) was replaced in the dissolution vessel to maintain the sink condition. The experiment was performed in triplicates, and the mean value was calculated.

In vitro permeation studies

A diffusion cell fabricated on the lines of Franz diffusion cell with an effective diffusional area of 4.906 cm^2 was used for these studies. Full thickness skin obtained from chest portion of human cadaver was used. Epidermis isolated by heat separation method[21] was used as the barrier and was then mounted between the receiver and the donor compartment of the diffusion cell in such a way that stratum corneum faces upward in the donor compartment. Once the skin was clamped between the donor and the receiver compartment and the receiver compartment was filled with phosphate-buffered saline solution (pH 7.4, 20 mL), then the whole assembly was kept in an oven preset at 32 ± 0.5°C and equilibrated until no UV absorbance was observed[14]. The patch to be tested was placed on the stratum corneum side of the skin. Skin was in intimate contact with the phosphate-buffered saline (pH 7.4) solution (receptor phase) and agitated with a magnetic stirrer throughout the study. The top of the cell was covered with aluminum foil to avoid drug photosensitivity. Samples (1 mL every time) were withdrawn at regular time intervals through the sampling port and fresh prewarmed receptor fluid solution was added. Absorbance of sample was measured spectrophotometrically at 236 nm against saline phosphate buffer (pH 7.4) as a blank[22,23]. Flux was determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg/cm^2) versus time in hours[24], and permeability coefficients were deduced by dividing the flux by initial drug load (mg/cm^2)[4].

Skin irritation studies

The hair on the dorsal side of Wistar albino rats was removed by clipping 1 day before the initiation of this study. The rats were divided into three groups (n = 6). Group I served as the control, group II received optimized transdermal patch, and group III received a 0.8% (v/v) aqueous solution of formalin as a standard irritant[24]. A new patch or new formalin solution was applied daily for 7 days. Finally, the application sites were graded always by the same investigator according to the method of Draize et al.[26] Prior permission was obtained from Institutional Animal Ethics Committee (IAEC) to carry out the irritation study.

Drug carrier interaction studies

The interaction studies were conducted on the optimized formulation by comparing it with pure drug and placebo formulation on the basis of UV, IR, and thin layer chromatography analysis[27].

Results and discussion

Damars are solid resins, generally less hard and durable than the Copals, are yellowish to grayish brown in color. Softening point of DB was found in the range of 90–93°C. Gel permeation chromatographic analysis of DB is shown in Figure 1. It was observed that DB has a narrow range of molecular weight distribution as indicated by the low polydispersity index (M_w/M_n). The DSC graph of DB shown in Figure 2 revealed that the glass transition temperature of DB is 38.79°C. DB was found to be practically insoluble in water and soluble in almost all organic solvents. Solubility profile of DB

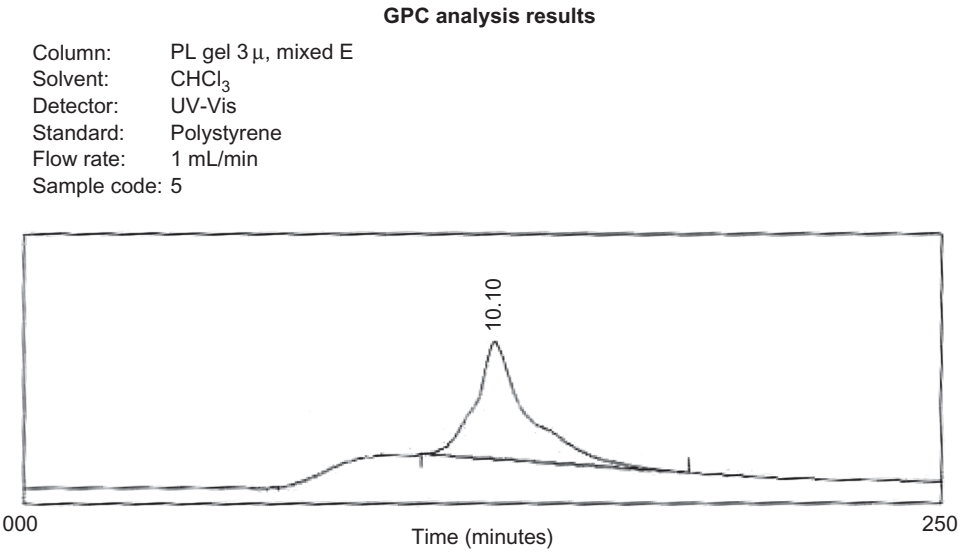

Figure 1. GPC Analysis of DB (M_n = 60, M_w = 120, and PI = 2).

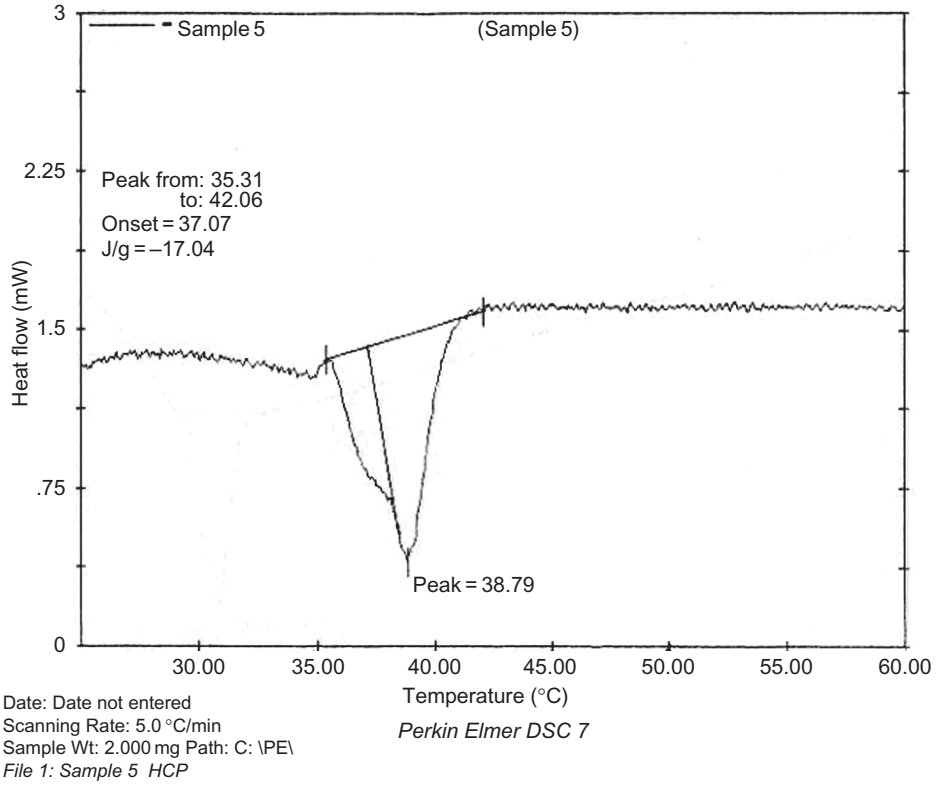

Figure 2. DSC graph of DB.

indicated its hydrophobic nature. The physicochemical properties of DB are summarized in Table 1.

Film characterization

Nonplasticized DB films were smooth and transparent but were very brittle, and hence addition of plasticizer was found to be essential to improve the mechanical properties of free films. Plasticizer shifts the glass transition temperature to lower temperature and is an important formulation factor[28]. Film characterization could not be carried out on nonplasticized films of DB, as films were brittle when dried. Because of the hydrophobic nature of DB, we employed DBS, a hydrophobic plasticizer in this study. DBS at 10% (w/w)

Table 1. Polymer characterization.

Parameter	Observation
Color	Grayish brown
Acid value[a]	27.08
Softening point[a]	90–93°C
Molecular weight (M_w)	120
Polydispersity index (PI = M_w/M_n)	2.0
Glass transition temperature (T_g)	38.79°C

[a]Represents the average of three determinations.

Table 2. Mechanical properties of the plasticized films.

Material	Thickness of film (μm)	Tensile strength (N/mm^2)	% elongation
DB with 20% DBS	0.27 ± 0.005	0.102 ± 0.31	21.944 ± 0.13
DB with 30% DBS	0.275 ± 0.001	0.217 ± 0.65	25.453 ± 0.17

Data represent mean ± SD of three determinations.

concentration failed to improve the film characteristics to a great extent, and hence mechanical properties of the plasticized DB films containing 20% and 30% (w/w) DBS, as shown in Table 2. DB films containing 30% (w/w) DBS were tough and showed excellent % elongation. DB films with DBS at more than 30% (w/w) concentration were found to be tacky, and hence all the formulations were developed using DBS as plasticizer at 30% (w/w) concentration (based on the total weight of the dry polymers).

Evaluation of transdermal patches

DH transdermal patches developed by mercury substrate technique using DB alone and in combination with ERL100 (Table 3) were evaluated for thickness and weight uniformity, folding endurance, and drug content. The thickness of the patches varied from 0.26 ± 0.002 to 0.31 ± 0.005 mm. The low values of standard deviation obtained for the physicochemical parameters indicated excellent uniformity of the patches (Table 4). The results of physicochemical characterization studies proved that the process adopted for casting the films in this investigation is capable of giving uniform drug content and minimum batch variability. A photograph of

Table 3. Composition of prepared patches.

Formulations	Ratio of DB/ERL100
F1	100:0
F2	90:10
F3	80:20
F4	70:30
F5	60:40
F6	50:50

All formulations contain 30% (w/w) dibutyl sebacate.

Table 4. Physicochemical characterization of the developed transdermal patches.

Formulation code	Thickness (mm) ± SD	Weight (mg) ± SD	% drug content ± SD	Folding endurance
F1	0.29 ± 0.008	85.5 ± 0.034	19.12 ± 0.06	13
F2	0.285 ± 0.005	83.4 ± 0.027	19.89 ± 0.12	15
F3	0.27 ± 0.001	87.8 ± 0.019	19.45 ± 0.98	17
F4	0.31 ± 0.005	82.6 ± 0.05	19.76 ± 0.55	18
F5	0.26 ± 0.002	84.8 ± 0.072	19.07 ± 0.85	23
F6	0.263 ± 0.02	86 ± 0.015	19.89 ± 0.37	24

Data represent mean ± SD of three determinations.

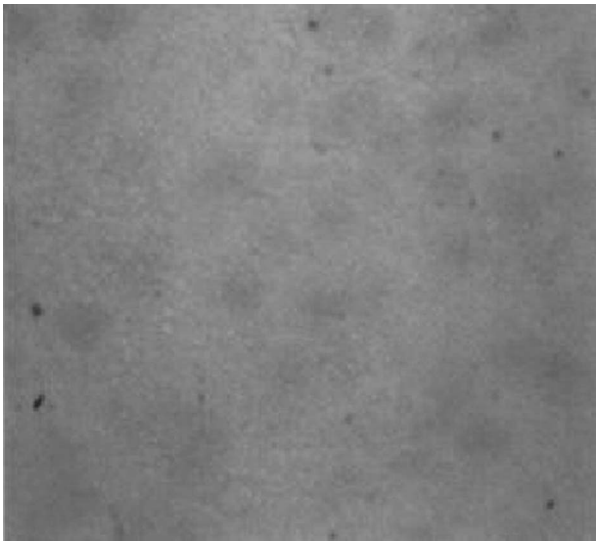

Figure 3. DB-free film surface (bright field microscope).

the surface of the optimized patch taken using bright field microscope (Leitz Laber Lux S-Microscope and CCD video camera) is shown in Figure 3. It was found that the surface of the transdermal patch was wrinkle-free and uniform in appearance. Folding endurance test results indicated that the patches would maintain the integrity with general skin folding when applied. It was observed that as the concentration of the ERL100 increased and concentration of DB decreased in the film formulation, the folding endurance increased.

In vitro drug release studies

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance[29]. For in vitro release studies, we employed a paddle-over-disk method (USP dissolution apparatus V). The results indicated that the release of drug from the patches increases with increasing concentration of ERL100 (Figure 4). Formulation F1 with DB

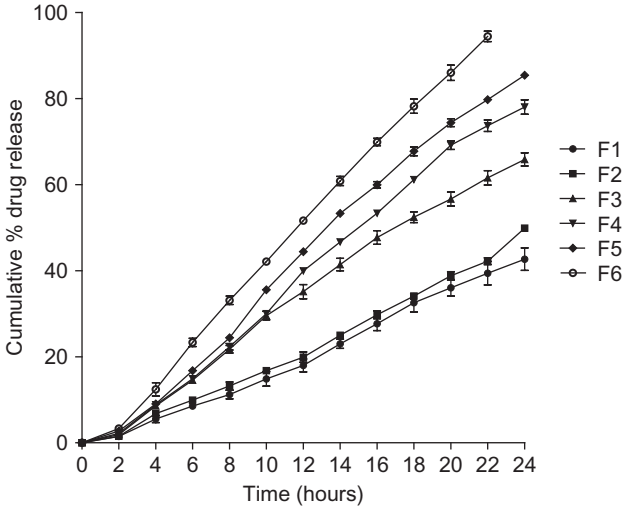

Figure 4. In vitro release profile of DH transdermal film formulations (mean ± SD of three independent experiments).

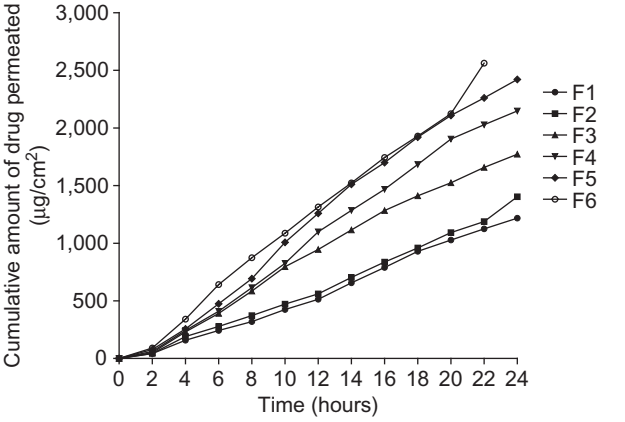

Figure 5. In vitro skin permeation profile of DH transdermal film formulations at 32 ± 0.5°C (mean ± SD of three independent experiments).

alone showed very less amount of drug released in 24 hours (45.67 ± 2.61%) when compared with other formulations, and the reason for low release of the drug from the patches developed with DB alone could be the hydrophobic nature of the polymer. Formulations F2–F5 were found to sustain the release of the drug for 24 hours. Formulation F6 developed with DB/ERL100 (50:50) showed highest amount of drug released (94.46 ± 1.22%) in 22 hours, and this formulation failed to sustain the release till the end of 24 hours. Release studies revealed that increase in the concentration of DB in the formulations decreases the release rate of the drug. Addition of increasing amount of ERL100 in the formulations (F2–F6) indicated increase in the drug release rate, and it was found very much in accordance with the explanation given by Bodmeier and Paeratakul[30] regarding the behavior of the drug release from the combination of the hydrophobic and hydrophilic polymer.

In vitro skin permeation studies

Release of drug from transdermal patches is controlled by the chemical properties of drug and delivery form as well as the physiological and physicochemical properties of the biological membrane[31]. Polymers play an important role in the transdermal drug delivery of DH as this drug has been shown to permeate the skin without the help of any penetration enhancer[12–14]. The in vitro permeation studies are predictive of in vivo performance of a drug[32]. Figure 5 shows the cumulative amount of DH permeated through the human cadaver skin, into a receptor solution, as a function of time from the various patches. The mean of cumulative amount of drug permeated (µg/cm^2 of the film) after 24 hours from the formulations F1, F2, F3, F4, and F5 was found to be 1217.6 ± 0.61, 1403.3 ± 1.09, 1772.2 ± 0.65, 2147.4 ± 2.27, and 2420.4 ± 0.31, respectively. Formulation F6 showed 2562.4 ± 0.63 µg drug permeation at the end of 22 hours and could not control the release till 24 hours. Cumulative amount of drug permeated (µg/cm^2 of patch) through the skin into the in vitro fluid plotted against time showed almost rectilinear curve of the data. The slope of these curves indicates the flux of the formulation, and it was found to be 0.066, 0.075, 0.086, 0.106, 0.125, and 0.129 for the formulations F1, F2, F3, F4, F5, and F6, respectively. The corresponding permeation coefficient values were 0.02, 0.022, 0.026, 0.031, 0.038, and 0.045. It is evident from these studies that skin permeation of the drug increased with increase of ERL100 content. The in vitro skin permeation experiments are known for their value for studying the rate and mechanism of percutaneous absorption of drugs[33]. The improvement in skin flux with the increase of ERL100 content may be because of its high water permeability property[34].

Skin irritation studies

The skin irritation test of the optimized transdermal formulations F5 showed a skin irritation score (erythema and edema) of less than 2 (Table 5). According to Draize et al., compounds producing scores of 2 or less are considered negative (no skin irritation). Hence, the optimized transdermal formulation is free of skin irritation. The skin irritation study results indicate that the polymeric patches are compatible with the skin and hence can be used for transdermal application.

Drug carrier interaction

Drug carrier interaction studies were carried out to ascertain any kind of interaction of the drug with the excipients used in the preparation of transdermal patch. R_f values for pure drug and formulation F5 were

Table 5. Skin irritation scores.

	Control		F5		Formalin	
Rat no.	Erythema	Edema	Erythema	Edema	Erythema	Edema
1	0	0	0	2	3	2
2	0	0	1	1	3	3
3	0	0	1	0	3	2
4	0	0	0	1	2	2
5	0	0	1	1	1	3
6	0	0	1	0	3	2
Average	0	0	0.66 ± 0.51	0.83 ± 0.75	2.5 ± 0.83	2.33 ± 0.51

Erythema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, scar formation. Edema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe.

proximal (0.78 and 0.72, respectively). UV absorption maxima for pure drug and formulation F5 was found to be 236 nm. Comparison of IR spectra of pure drug and F5 showed that the entire major absorption peaks of DH were intact. All these results indicated that the drug remained intact in the formulation and there was no chemical interaction between the drug and the carrier.

Summary and conclusion

We can conclude from the results of this work that DB in combination with ERL100 with the incorporation of DBS (30%, w/w) produces smooth and flexible film, which was found to control and prolong the drug release till 24 hours. The release rate of the drug from films and permeation across skin increases with increase in ERL100 loading. Patches containing DB/ERL100 (60:40) show promise for pharmacokinetic and pharmacodynamic performance evaluation in a suitable animal model. In view of the overall results reported in this study, it can be proposed that DB is suitable matrix-forming agent for the design of transdermal drug delivery system.

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