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Primaquine-loaded transdermal patch for treating malaria: design, development, and characterization

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Abstract

Background: The goal of the current study was to create, improve, and test a transdermal patch loaded with primaquine for the treatment of malaria. Several ingredients were used to create the transdermal patch. For the choosing of polymers, placebo patches were created. The optimization of polymer ratios for patch development and testing their impact on tensile strength, in vitro drug release, in vitro drug permeation, and ex vivo drug permeation employed response surface methods. The F5 formulation was chosen as the optimal formulation based on these answers to the data. The stability of the F5 formulation was examined. According to the findings of trials on acute skin irritation, no place where transdermal patches were given showed any signs of clinical abnormalities or a change in body weight. No erythema or edema of the skin was seen in the rabbit's skin.

Results: It was observed that tensile strength of the transdermal films formulated with Eudragit RL100 and hydroxypropyl methylcellulose (P_{mix}) was found between 0.32 ± 0.017 and 0.59 ± 0.013 kg/cm^2, which were 0.32 ± 0.017 (F1), 0.36 ± 0.012 (F2), 0.35 ± 0.015 (F3) for P_{mix} ratio 1:1, 0.42 ± 0.011 (F4), 0.49 ± 0.010 (F5), 0.55 ± 0.016 (F6) for P_{mix} ratio 1:2 and 0.56 ± 0.014 (F7), 0.57 ± 0.010 (F8), 0.59 ± 0.013 (F9) for P_{mix} ratio 1:3. Data fitting to the Peppas, Hixon–Crowell, Higuchi, and Zero-order models was used to examine the optimized transdermal patch (F5) release kinetic mechanism. Data comparison was done using the correlation coefficient (R^2). Zero-order had an observed correlation coefficient (R^2) of 0.9988, which was greater than that for other models. Therefore, it was clear that the medication was released from the formulation after the Zero-order release.

Conclusion: The ideal thickness, percent elongation, and tensile strength of the primaquine therapeutic transdermal patches were prepared for transdermal delivery. The therapeutic transdermal patch was prepared by using Eudragit RL100: HPMC K15M (1:2) into the patch because this combination was responsible for the significant delivery of the drug into the bloodstream. The therapeutic transdermal patch has a notable penetration rate. Dimethyl sulfoxide was used as a permeation enhancer, which helped to obtain a high penetration rate. The statistical analysis was used to support the improved formulation. The therapeutic transdermal patch is a potential vehicle for the administration of primaquine, according to stability studies.

Keywords: Primaquine, Malaria, Transdermal patch, Optimization, ANOVA

Introduction

From ancient time, malaria has been a lethal illness. When studying Indian history, we may find several old medical texts, such as the Charaka Samhita and the Atharva Veda, which describe malaria in depth [1]. At the time of its independence in 1947, India had 330 million residents altogether, 75 million of whom had

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malaria every year. Because of malaria infection, there were 0.8 million deaths directly related to the disease per year [2, 3]. According to estimates, 1.2 billion individuals are at very high risk of contracting malaria, which affects an estimated 3.2 billion people globally. The severity of the crisis has increased as a result of the malaria parasites' growing resistance to antimalarial drugs.

In the liver phase of malaria parasites, primaquine is used to combat schizonticides in pre-erythrocytic tissue (*Plasmodium vivax* and *Plasmodium ovale*). Primaquine is a gametocytocidal drug that may also be used to treat the exoerythrocytic stage of an infection. The only 8-amino quinolone drug that has the potential to successfully treat parasites in their hepatic stages is this one. Numerous recent researches suggest that the malaria parasites *Plasmodium vivax* and *Plasmodium falciparum* can be treated with primaquine as a prophylactic drug. Primaquine is more successful than chloroquine for treating *Plasmodium vivax* and *Plasmodium falciparum*, according to the study [4]. Sharma P and Tailang M state that primaquine has preventative advantages and should only be stopped seven days after the recipient leaves an endemic area, although there have also been reported cases of mild to severe GIT discomfort [5]. In the absence of the enzyme glucose-6-phosphate dehydrogenase, primaquine is not utilized. However, the therapeutic transdermal delivery method may be able to mitigate some of the adverse effects of primaquine when compared to traditional dosage forms like tablets, including stomach discomfort, hepatological drug metabolism, and other dose-dependent consequences. Adhesive patch medication solution, suspension, or emulsion is trapped in a semisolid matrix and in direct contact with a release liner in the matrix [6, 7]. A suitable carrier through the transdermal drug delivery method is a transdermal patch loaded with primaquine. Drugs that undergo a lot of hepatic metabolism might benefit greatly from any transdermal penetration into the circulation, which bypasses liver metabolism. Additionally, for medications that have a considerable portion of absorption in the oral cavity and pregastric segments of the GIT as well as for pharmaceuticals that create significant amounts of hazardous metabolites mediated by liver metabolism and gastric metabolism, safety profiles may be enhanced. In the current study, we created a primaquine-loaded therapeutic transdermal patch and looked at how well the drug permeated both in vitro and ex vivo. The prepared formulation has a transdermal effect so primaquine will act after reaching systemic circulation.

Methods

Primaquine was procured as a gift sample from ITL Labs, Indore, Madhya Pradesh, India. Castor oil I.P. was purchased from the chemist shop (Mfg. by Search Creation Company). HPMC and Ethylcellulose were procured from Himedia Laboratories Pvt. Ltd., Delhi, India. Eudragit RL100 and Eudragit RS100 were procured from Central Drug House (P) Ltd., Daryaganj, New Delhi, India. Solvents, water, and other chemicals were used in analytical grade. New Zealand White rabbit was used to evaluate skin sensitivity test and New Zealand White rabbit was procured from Chakraborty Enterprise, Dandirhat, Basirhat, North 24 Parganas, West Bengal, India. The animal experimental studies were approved by IAEC (Institutional Animal Ethical Committee) as per the regulation committee for CPCSEA (Control for Purpose of Control and Supervision of Experiments on Animals) Government of India and registration number of approval was IAEC/JU/47.

Preformulation studies

Physical appearance

Visual examination was used to determine primaquine's physical characteristics.

The infrared spectral determination of drug

FT-IR may be used to identify unidentified elements, assess the quality or consistency of a sample, and count the number of ingredients in a combination. Utilizing potassium bromide (KBr) powder, and FT-IR spectra of medication samples was obtained from 400 to 4000 cm^{-1}. The sample (Drug: KBr-5:95) was put into a sample holder before their infrared absorption spectra were taken. Therefore, FT-IR spectra have been investigated for the qualitative identification of drug sample. The drug's infrared spectrum was then measured and contrasted with the industry norm [8, 9].

Melting point determination of drug by differential scanning calorimetry (DSC)

Utilizing differential scanning calorimetry (DSC) with a preset heat rate of 10 °C per minute, the melting temperature of primaquine was determined. Primaquine sample (~ 5 mg) was heated between 185 and 215 °C using dry nitrogen flows at a scanning rate of 10 °C min^{-1} in crimped aluminum pans.

Incompatibility study

The drug and polymer interaction was evaluated through infrared spectroscopy. A straightforward way for finding changes in drug-excipient combinations

is FT-IR. The occurrence of interactions between the API and the investigated excipient is indicated by the removal of an absorption peak, a decrease in peak strength, or the formation of additional peaks [8, 9]. An FT-IR spectrum of drug samples was done by FT-IR (IR Affinity-1, Shimadzu, Japan) from 400 to 4000 cm^{-1} by using potassium bromide (KBr) powder.

Formulation of different placebo polymeric patches for selection of polymer

By combining distinct hydrophobic and hydrophilic polymer combinations, several placebo transdermal patches were created [10, 11]. A combination that demonstrated the best abilities to support a transdermal administration of medicines was chosen for manufacture from among these variously constructed placebo patches. By utilizing different polymers in different ratios, the composition and characterization of placebo patches are shown in (Table 1).

Optimization of primaquine-loaded transdermal patch by 3^2 factorial designs

The purpose of the 3^2 factorial design (3^2−2 variables at three levels) was to select the stages of different independent variables (Table 2) of P_{mix} ratio (R_1) and DMSO concentration (R_2) with tensile strength (Y_1), in vitro drug release profile after 72 h (Y_2), and ex vivo skin drug permeation after 72 h (Y_3).

Fabrication of primaquine containing loaded transdermal patch

Solvent evaporation methods were used to create transdermal patches of the matrix type that were filled with primaquine. A petri dish with a diameter of 10 cm and a surface area of 78.5 cm^2 was employed. Weighing was done using the following ratios of Eudragit RL100 and HPMC K15M (Pmix ratio): 1:1 (150 mg and 150 mg), 1:2 (100 mg and 200 mg), and 1:3. (75 mg and 225 mg). The weighted amounts were then dissolved in 10 ml of a 1:1 ethanol to water solution and set aside to create a clear solution.

Table 1 Composition of several placebo polymeric patches for polymer selection

Batch code	Polymer	Ratio	Solvent	Physical appearance
PC1	Eudragit RL100: Eudragit RS100	1:2	Ethanol: Water	Non-uniform
PC2	Eudragit RS100: Eudragit RL100	1:2	Ethanol: Water	Non-uniform
PC3	Eudragit RL100: HPMC K15M	1:2	Ethanol: Water	A transparent, smooth, flexible, uniform film
PC4	HPMC K15M: Eudragit RL100	1:2	Ethanol: Water	A transparent, somewhat rigid, flexible, uniform film
PC5	Eudragit RS100: HPMC K15M	1:2	Ethanol: Water	A transparent, flexible with small clumps
PC6	HPMC K15M: Eudragit RS100	1:2	Ethanol: Water	A transparent, flexible with small clumps
PC7	Eudragit RL100: EC	1:2	Ethanol: Water	Brittle and non-uniform
PC8	EC: Eudragit RL100	1:2	Ethanol: Water	Brittle and non-uniform
PC9	Eudragit RS100: EC	1:2	Ethanol: Water	Brittle and non-flexible
PC10	EC: Eudragit RS100	1:2	Ethanol: Water	Brittle and non-flexible
PC11	HPMC K15M: EC	1:2	Ethanol: DCM	Non-uniform
PC12	EC: HPMC K15M	1:2	Ethanol: DCM	Non-uniform

Table 2 Actual unit with coded labels (3^2 factorial designs)

Factors	Level used		
	Level-1 (Low)	Level 0 (Medium)	Level 1 (High)
Independent variables			
$R_1 = P_{mix}$	1:1	1:2	1:3
R_2 = DMSO Conc. (w/w) of total polymer	10	15	20
Dependent variables			
Y_1 = Tensile strength (TS)			
Y_2 = In vitro drug release			
Y_3 = Ex vivo drug permeation			

Table 3 Composition of a transdermal patch according to factorial design

Formulation code	Components (% w/w of total polymer weight of 300 mg)				
	Primaquine	P_{mix} (R_1)	DMSO (R_2)	Plasticizer (PEG 400)	Solvent (Ethanol: Water)
F1	100 (300 mg)	1:1 (− 1)	10 (− 1)	30	1:1
F2	100 (300 mg)	1:1 (− 1)	15 (0)	30	1:1
F3	100 (300 mg)	1:1 (− 1)	20 (1)	30	1:1
F4	100 (300 mg)	1:2 (0)	10 (− 1)	30	1:1
F5	100 (300 mg)	1:2 (0)	15 (0)	30	1:1
F6	100 (300 mg)	1:2 (0)	20 (1)	30	1:1
F7	100 (300 mg)	1:3 (1)	10 (− 1)	30	1:1
F8	100 (300 mg)	1:3 (1)	15 (0)	30	1:1
F9	100 (300 mg)	1:3 (1)	20 (1)	30	1:1

In the formulation, 30% weight percent (w/w) of total polymer polyethylene glycol was used as a plasticizer, and 15% weight percent (w/w) of total polymer DMSO was utilized to increase penetration (Table 3). Before casting the polymer, the uniform solutions that had been developed were cast onto a Petri plate using a suitable lubricant (glycerine) to enable film separation. Inverted funnels were put on top of the Petri plate to limit the pace at which solvents evaporated. The dried films were removed from the Petri plate after 24 h and stored for further characterization in a desiccator [12].

Characterization of primaquine-loaded transdermal patch

Physical appearance

Patient acceptance of these patches can be judged based on physical homogeneity, appearance, drug precipitation, or trapping of any air bubble characteristics of the prepared patches [13].

Thickness

The Mitutoyo Digimatic Micrometer was used to measure the transdermal film thickness (Model: 293-821-30). Four-by-three-cm rectangular patches were measured at three separate locations, and the mean thickness was computed. Each film's thickness shouldn't differ greatly from other patches in terms of thickness [13].

Weight variation

By weighing 10 patches (each one separately) chosen at random, weight variations were identified. The mean weight was then computed. Individual patch weights shouldn't vary considerably from the mean weight [13, 14].

Surface pH

Primaquine-loaded films were left in double-distilled water for 0.5 ml to facilitate swelling. The pH was measured using positive and negative glass electrodes. After giving the electrodes a minute to acclimate, the pH of the film was measured with these electrodes close to the surface.

Swelling index

The primaquine-loaded films were cut into 4×3 cm and weighed (W_0). After that, it was dipped in distilled water (5 ml) at room temperature for 24 h. An excess amount of distilling water was removed from the aqueous sample and it was reweighed (W_s). The swelling index was calculated using the following formula.

$$\left(\text{Swelling Index } (\%) = \frac{(W_s - W_0)}{W_0} \times 100\right)$$

Folding endurance

To determine the capability of patch folding, folding endurance was assessed. The size of the film was measured manually and folded repeatedly until it broke into a 4×3 cm strip. The number of times a patch may be folded at one location without breaking or cracking should fall within the range [15].

Tensile strength

Polymeric patches' mechanical qualities made it simple to assess their tensile strength [16, 17]. An assembly that must be assembled manually was created to determine the film's tensile strength. An end of the strong thread was attached to the center of the film, while the other end was used to suspend the pan. Utilizing plastic clips, the transdermal film was secured. A hanging pan

with set weights was preserved in the intended arrangement, which resembled a beam balance. It was noted what was necessary to break the film.

The tensile strength of transdermal films was calculated by using the following equation:-

$$\text{Tensile Strength} = \frac{F}{A \times B\ (1 + \Delta L/l)}$$

where F (Break force) is the weight required for breaking the film (Kg), A is the width of the film, B is the thickness of the film, ΔL is the elongation of the film at a breakpoint and l is the length of the patch.

Percent elongation test

The film's length (4 cm) was noted before to the % elongation break test, and the percentage was computed using the formula below.

$$\text{Elogation Percentage} = \left[\frac{(L_1 - L_2)}{L_2}\right] \times 100$$

where L_1 is the length of the film after elongation and L_2 is the length of the individual film before the elongation.

Percent of moisture content

Each of the prepared patches was weighed before being placed in a Petri plate and placed in a desiccator with fused $CaCl_2$ for a 24-h period. The patches were weighed again after 24 h, and the method below was used to calculate the percentage of moisture content [18].

$$\text{Pecentage Moisture Content} = \left[\frac{(\text{Initial Weight} - \text{Final Weight})}{\text{Final Weight}}\right] \times 100$$

Percentage moisture uptake

To maintain 84% relative humidity, the developed patches were weighed separately, placed in a Petri plate, and the Petri plate was then placed in a desiccator with a saturated KCl solution. The patches were reweighed after 24 h and using the method below, the percentage of moisture content was determined [18].

$$\text{Pecentage Moisture Uptake} = \left[\frac{(\text{Final Weight} - \text{Initial Weight})}{\text{Initial Weight}}\right] \times 100$$

Water vapor transmission rate (WVTR)

The transmission cells for the water vapor were made of glass vials with equal diameters. A prepared patch was fastened as a cover over the brim and 1 g of calcium chloride anhydrous was inserted into the cells. The cells were weighed and stored in a desiccator with an $AlCl_2$ solution that was saturated to maintain an environment with a relative humidity of 84%. At predetermined intervals (6, 12, 24, 36, 48, and 72 h), the transmission cells were removed and weighed again to determine the WVTR using the formula below [18].

$$\text{WVTR} = \left[\frac{(\text{Final Weight} - \text{Initial Weight})}{\text{Exposure Time} \times \text{Area of Film}}\right] \times 100$$

Drug content uniformity

To ascertain the amount of medicine entrapped in a transdermal film, a 4×3 cm piece of it was totally dissolved in a 7.4 pH phosphate buffer solution (100 ml). The film disintegrated after being shaken with the solution for 24 h. The drug concentration was then ascertained from this solution using a UV–VIS spectrophotometer at 259 nm with a reference being a pH 7.4 phosphate buffer solution.

In vitro drug release from the transdermal film

A modified stainless steel disk assembly is used in the USP dissolution type 5 device [19]. For testing, a rectangular patch measuring 4 by 3 cm and containing 16.64 mg of primaquine was employed. The dissolving device was calibrated using PBS pH 7.4 at a temperature of 37 ± 0.5 °C and 100 rpm. Samples were taken out at the proper intervals, and their absorbance was measured using UV–VIS spectroscopy at 259 nm. The cumulative % of drug release was then calculated and plotted against time. For the determination of mechanism and kinetics of drug release, the data of drug release were using Higuchi, Korsmeyer-Peppas, Hixon-Crowell, First-order, and Zero-order kinetic models. Then the values of the correlation coefficient were calculated from the linearity of curves [20].

Ex vivo flux (µg/cm2/hrs)

Ex vivo skin flux is the amount of drug permeation through the predefined size of skin at fixed time intervals. The permeation profile of the drug can be analyzed by steady-state flux or slope of the curve. Ex vivo flux or steady-state flux is calculated by the following formula:

$$\left(\text{Ex}-\text{vivo flux}=\frac{[\text{Conc.at calculation point (hour)}-\text{Conc.at previous point (hour)}]}{\text{Time interval}\times\text{Total drug Conc.in patch}\times\text{Patch size}}\right)$$

Ex vivo skin permeation study

Franz diffusion cell was used for ex vivo skin permeation study with an effective diffusion area of 4 × 3 cm. On the excised dorsal side skin of the Wistar rat, the sample was placed and tied between the donor and receptor part of Franz diffusion cell and stratum corneum side of skin toward the donor compartment. Then 16.64 mg loaded transdermal film was applied to the donor part of the cell. The PBS 7.4 pH solution was filled in the receptor compartment and the temperature was maintained at 37 °C ± 0.5 °C. At the fixed time interval sample were withdrawn [20]. After that, all samples were filtered and assayed by a UV spectrophotometer at 259 nm. For the determination of the mechanism and kinetics of drug release, the data of drug release were used Higuchi, Korsmeyer–Peppas, Hixon–Crowell, First-order, and Zero-order kinetic models. Then the values of the correlation coefficient were calculated from the linearity of curves [21].

Statistical analysis

One-way analysis of variance (ANOVA) was used for statistical analysis of data collected from evaluated formulations.

Skin sensitivity test

A skin irritancy test was conducted on a 2–3.5 kg weighted male healthy rabbit (New Zealand White rabbit). According to OECD (Organisation for Economic Co-operation and Development), guideline 404, housing conditions were maintained before the test. As per OECD, guideline 404 skin sensitivity test was performed. Approximately 24 h before the test, hairs of the left dorsal skin and right dorsal skin of the rabbit were shaved and removed without affecting the skin. USP-type adhesive tape was applied as a control patch. The transdermal patch of 4 × 3 cm was applied as a test sample. The skin sensitivity test was performed on unbraid skin of rabbits; the standard (control film) patch was applied on the left dorsal surface of the rabbits, whereas primaquine-loaded transdermal film was applied on a similar side of the right dorsal surface of rabbits. The film was detached after 1, 24, 48 and 72 h by using swab of alcohol, and the left dorsal surface and right dorsal surface of the rabbit's skin were examined for any edema and erythema [22, 23].

Edema and erythema were scored on a 0–4 scale, where 0 denotes no effect and 4 showing severe symptoms. For every testing site, skin response scores at 1, 24, 48, and 72 h after the detachment of the films were summed and divided by three to observed mean sensitivity score/time point. The results were compared to those sites where a control film was applied. The average scores were summed and mean to obtain the initial irritation index.

Stability study

The stability is essential for pharmaceutical products to evaluate its various properties to decide its shelf-life [22, 24]. The main aim of the stability test was: (I) selection of suitable preparation and (II) shelf-life determination and storage conditions for transdermal films [24]. After the test rabbit was observed for reversibility of the effects. To determine the reversibility of effects, the rabbit was observed for 14 days after the removal of patches. Then the rabbit was rehabilitated at general required conditions (as per OECD guideline 404).

Results

Preformulation studies

Physical appearance

Based on visual inspection, the physical appearance of primaquine was revealed as an odorless orange powder.

The infrared spectral determination of drug

When the primaquine IR spectra were matched to the norm, the existence of several groups was established. Figure 1 displays the different peaks found in the IR spectra, including aromatic C=C stretching at around 1532 cm^{-1} and 1467 cm^{-1} and NH_2 bending at 1614 cm^{-1}.

Melting point determination of drug by differential scanning calorimetry (DSC)

DSC thermograms of primaquine showed three exothermic peaks one of which at 195.48 °C corresponding to the melting point of the primaquine and another at 127.81 °C due to bond loosening of primaquine and the third peak at 205 °C due to solid–liquid phase transition was depicted in Fig. 2.

Incompatibility study

When compared to a standard, the IR spectra of primaquine, HPMC K15M, and Eudragit RL 100 showed no removal of an absorption peak, no decrease in peak intensity, and no emergence of new peaks, proving that there was no interaction between the various groups of pharmaceuticals and polymers as depicted in Fig. 3.

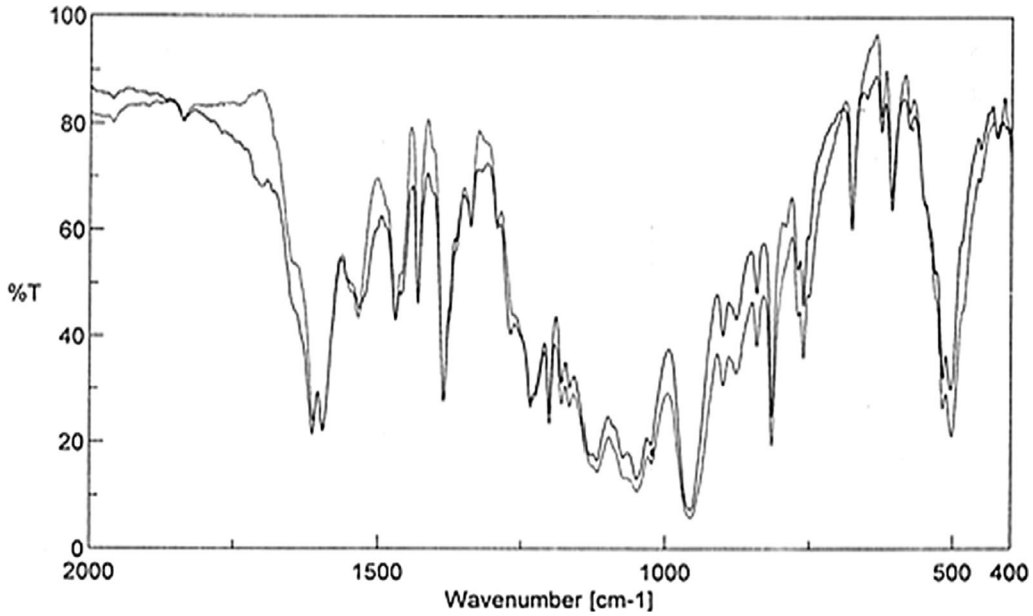

Fig. 1 FT-IR spectrum of primaquine

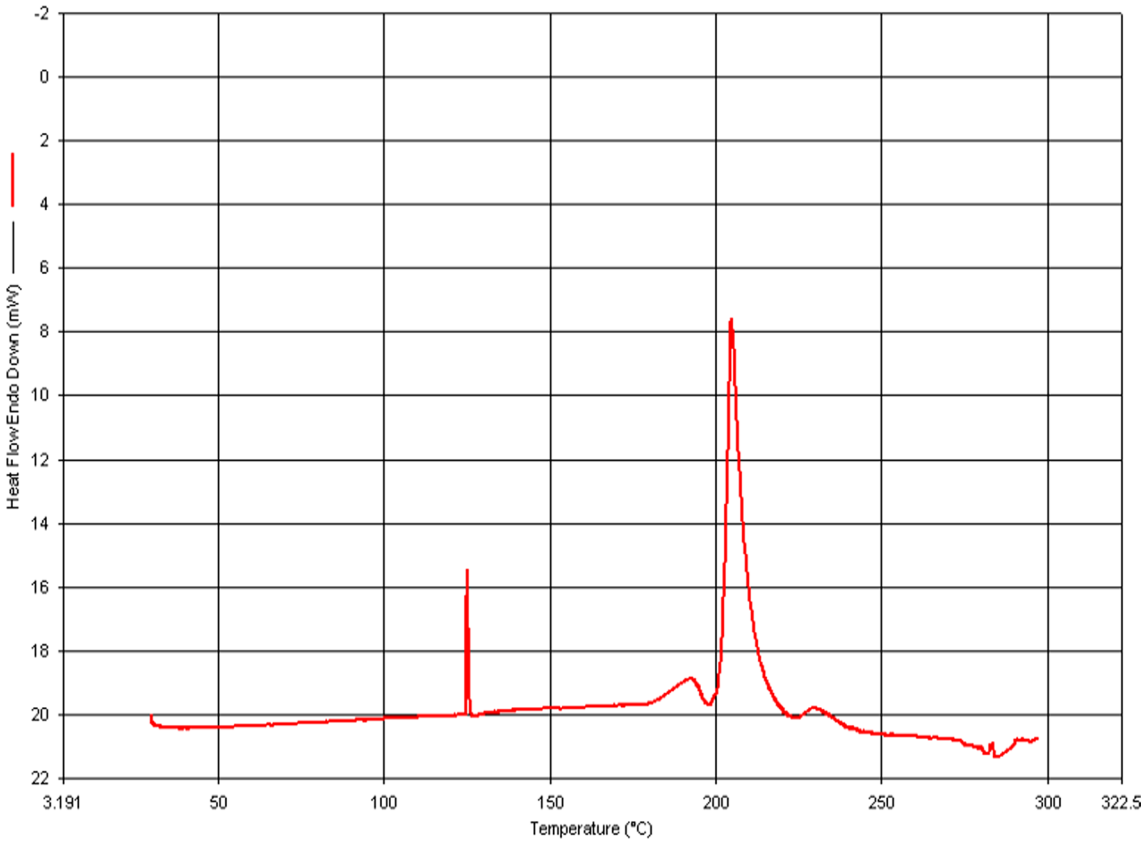

Fig. 2 DSC graph of primaquine

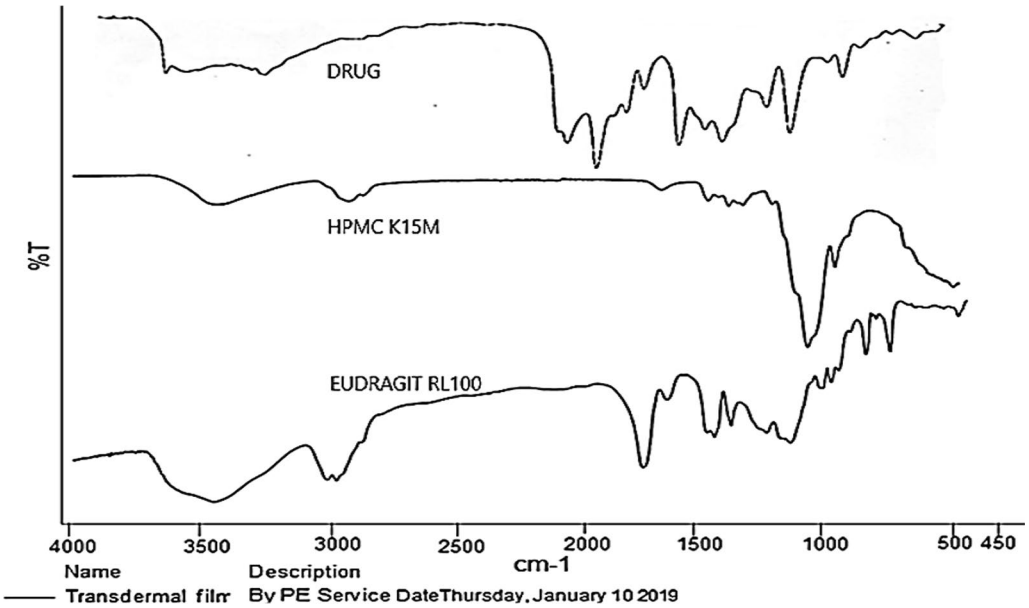

Fig. 3 IR graph of polymer matrix type transdermal patch

Fabrication of primaquine-loaded transdermal patch

The created patch was pliable, transparent, and stable over time. Large amounts of HPMC were used as a parent polymer because it had a significant impact on medication absorption and release. Without changing the drug release profile, a transparent, flexible patch was created using PEG 400 at a concentration of 30% by weight of the entire polymer. Patches lose their flexibility and stiffen up if the plasticizer concentration is more than 30% w/w of the overall polymer concentration.

Physical appearance

The transdermal patch for primaquine had a smooth surface and a translucent yellowish tint, while the patch for the placebo had a clear, transparent color.

Thickness

The primaquine-loaded transdermal films' thicknesses ranged from 0.32 to 0.52 mm in all formulations. Due to Eudragit RL100's lower solubility in water, the excessive thickness of formulations F6 and F4 may have resulted in an unbalanced distribution of the polymer layer. The uniformity of the transdermal films was shown by the low value of the standard deviation (SD) (Table 4).

Weight variation

Average weight of 10 films for F1, F2, F3, F4, F5, F6, F7, F8 and F9 was 500, 510, 498, 502, 507, 505, 490, 501 and 504, respectively, and percentage deviations for these formulations were 4.6%, 3.92%, 3.81%, 4.18%, 4.33%, 4.36%, 4.08%, 4.79% and 4.36%, respectively. Percentage weight

Table 4 Data for various evaluated parameters of transdermal films

Batch code	PA	Thickness (mm)	Weight variation (mg)	% Swelling index	Folding endurance (Numbers)	Tensile Strength (Kg/cm^2)	% Elongation
F1	TSFU	0.46 ± 0.03	500 ± 23	70.56 ± 2.3	190 ± 8	0.32 ± 0.017	40.7 ± 0.09
F2	TSFU	0.38 ± 0.04	510 ± 20	67.29 ± 3.1	193 ± 7	0.36 ± 0.012	38.4 ± 0.10
F3	TSFU	0.39 ± 0.03	498 ± 19	78.30 ± 5.0	187 ± 10	0.35 ± 0.015	42.3 ± 0.14
F4	TSFU	0.48 ± 0.03	502 ± 21	59.66 ± 4.3	196 ± 8	0.42 ± 0.011	47.9 ± 0.11
F5	TSFU	0.42 ± 0.02	507 ± 22	71.68 ± 4.1	190 ± 7	0.49 ± 0.010	37.8 ± 0.09
F6	TSFU	0.52 ± 0.04	505 ± 22	69.09 ± 2.9	199 ± 9	0.55 ± 0.016	39.3 ± 0.12
F7	TSFU	0.45 ± 0.02	490 ± 20	65.87 ± 4.3	189 ± 9	0.56 ± 0.014	38.6 ± 0.10
F8	TSFU	0.32 ± 0.03	501 ± 24	70.55 ± 3.7	192 ± 8	0.57 ± 0.010	46.1 ± 0.13
F9	TSFU	0.45 ± 0.04	504 ± 22	79.08 ± 4.5	191 ± 9	0.59 ± 0.013	40.2 ± 0.12

Values are shown as mean ± SD ($n = 3$)

variations for all formulation were in acceptable limits and shown in Table 4.

Swelling index

As expressed in Table 4**,** the swelling index was minimum for F4 (59.66 ± 4.3%) and maximum for F9 (79.08 ± 4.5%). The swelling index shows the hydration of patches when it was immersed in aqua. Enhanced hydration of polymers in patches leads to the creation of void spaces which may influence the sustained release profile of the matrix type of patch. The values of the swelling index for all formulations were depicted in (Table 4).

Folding endurance

The folding endurance for all factorial design films was observed as satisfactory which denotes that the films formulated using polyethylene glycol 400 in a 30% w/w of polymer concentrations were found optimum flexibility and were not brittle. Folding endurance for F1, F2, F3, F4, F5, F6, F7, F8, and F9 was 190 ± 8, 193 ± 7, 187 ± 10, 196 ± 8, 190 ± 7, 199 ± 9, 189 ± 9, 192 ± 8, and 191 ± 9, respectively. Folding endurance for all formulations was within acceptable limits (Table 4).

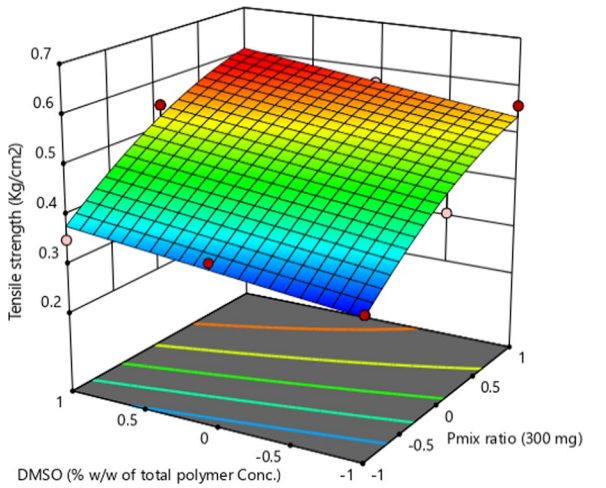

Fig. 4 Response surface plot of tensile strength

Tensile strength

The tensile strength of the transdermal films formulated with Eudragit RL100 and HPMS K15 was observed in between 0.32 ± 0.017 kg/cm^2 and 0.59 ± 0.013 kg/cm^2, which were 0.32 ± 0.017 (F1), 0.36 ± 0.012 (F2), 0.35 ± 0.015 (F3) for P_{mix} ratio 1:1, 0.42 ± 0.011 (F4), 0.49 ± 0.010 (F5), 0.55 ± 0.016 (F6) for P_{mix} ratio 1:2, and 0.56 ± 0.014 (F7), 0.57 ± 0.010 (F8), 0.59 ± 0.013 (F9) for P_{mix} ratio 1:3. It was found that with the increase in the concentration of HPMC K15, the tensile strength of films gradually decreased (Table 4). The data of tensile strength (response 1) of the transdermal film were fitted to different models by the application of response surface methodology and linearity was observed in the best-fitted model (Fig. 4).

Percentage elongation test

The percentage of elongation was observed to be in the range of 37.8 ± 0.09% to 47.9 ± 0.11%. The preparation F5 showed minimum (37.8 ± 0.09%) percentage elongation among the other factorial design preparations. It indicates that percentage elongation and tensile strength have an inverse relation. Percentage elongation for all formulations was within acceptable limits as shown in Table 4.

Water vapor transmission rate (WVTR)

The WVTR of formulated films ranged from 0.148 ± 0.01 to 0.280 ± 0.02 (g/cm^2/72 h) indicating that all films have permeability for water vapor. The low WVTR is an indication of the good stability of transdermal films in long-term storage (Table 5).

Table 5 Water vapor transmission rate of transdermal patch (F1–F9)

Batch code	Initial wt. (g)	Wt. after 6 h	Wt. after 12 h	Wt. after 24 h	Wt. after 36 h	Wt. after 48 h	Wt. after 72 h	WVT (g)	WVTR (g/cm^2/72 h)
F1	50.79 ± 1.1	50.98 ± 1.3	51.18 ± 1.4	51.46 ± 1.3	51.72 ± 1.4	51.96 ± 1.4	52.07 ± 1.5	1.28 ± 0.09	0.148 ± 0.01
F2	50.36 ± 1.3	50.54 ± 1.1	50.75 ± 1.3	51.09 ± 1.2	51.36 ± 1.3	51.61 ± 1.4	51.81 ± 1.5	1.45 ± 0.08	0.167 ± 0.02
F3	50.56 ± 1.2	50.76 ± 1.4	50.97 ± 1.5	51.37 ± 1.4	51.65 ± 1.5	51.80 ± 1.2	52.01 ± 1.3	1.45 ± 0.07	0.167 ± 0.02
F4	50.19 ± 1.1	50.38 ± 1.1	50.58 ± 1.1	50.96 ± 1.3	51.21 ± 1.2	51.45 ± 1.4	51.64 ± 1.4	1.45 ± 0.08	0.167 ± 0.01
F5	50.83 ± 1.1	51.01 ± 1.1	51.20 ± 1.2	51.61 ± 1.1	51.93 ± 1.3	52.14 ± 1.2	52.37 ± 1.3	1.54 ± 0.07	0.178 ± 0.01
F6	50.33 ± 1.1	50.43 ± 1.1	50.64 ± 1.3	51.05 ± 1.3	51.34 ± 1.4	51.54 ± 1.3	51.73 ± 1.3	1.40 ± 0.08	0.162 ± 0.02
F7	50.65 ± 1.3	50.83 ± 1.3	51.03 ± 1.4	51.42 ± 1.2	51.71 ± 1.3	52.93 ± 1.5	52.13 ± 1.3	1.48 ± 0.07	0.171 ± 0.02
F8	50.45 ± 1.3	50.66 ± 1.4	51.87 ± 1.3	52.22 ± 1.4	52.48 ± 1.4	52.68 ± 1.3	52.87 ± 1.4	2.42 ± 0.08	0.280 ± 0.02
F9	50.89 ± 1.2	51.09 ± 1.2	51.30 ± 1.5	51.71 ± 1.2	51.97 ± 1.5	52.16 ± 1.3	52.27 ± 1.2	1.38 ± 0.07	0.159 ± 0.03

Table 6 Data for various evaluated parameters of transdermal patch (F1–F9)

Batch code	Surface pH	% Moisture content	% Moisture uptake	% Drug content
F1	5.7 ± 0.11	05.11 ± 0.03	10.67 ± 0.33	98.48 ± 0.9
F2	5.5 ± 0.13	05.83 ± 0.02	10.98 ± 0.50	98.76 ± 0.7
F3	5.5 ± 0.12	05.96 ± 0.04	11.08 ± 0.46	99.00 ± 0.8
F4	5.6 ± 0.10	06.55 ± 0.06	11.29 ± 0.39	98.66 ± 0.9
F5	5.5 ± 0.12	06.76 ± 0.04	12.64 ± 0.41	99.10 ± 1.0
F6	5.5 ± 0.13	07.56 ± 0.03	13.01 ± 0.44	98.09 ± 0.9
F7	5.8 ± 0.12	07.87 ± 0.03	12.99 ± 0.29	98.87 ± 0.8
F8	5.4 ± 0.11	08.78 ± 0.05	13.24 ± 0.19	99.01 ± 0.9
F9	5.3 ± 0.14	09.99 ± 0.02	13.89 ± 0.48	98.88 ± 0.9

Surface pH

The pH of the transdermal film formulated with various ratios of polymers was observed at 5.3–5.8. The preparation F5 showed a minimum (5.5 ± 0.12) pH among the other factorial design preparations. It indicates that the pH of all formulated transdermal films was nearly identical to skin pH (Table 6).

Percentage of moisture content

The percentage of moisture content in transdermal films ranged from 05.11 ± 0.03 to 09.99 ± 0.02%. The percentage moisture content of the films was observed to be increased by the increase in the concentration of HPMC K15, and the percentage moisture content of all films was satisfactory (Table 6).

Percentage moisture uptake

The % moisture uptake of transdermal films was in the range (of 10.67 ± 0.33–13.89 ± 0.48%). The % moisture uptake of transdermal films was observed as F1 (10.67 ± 0.33%), F2 (10.98 ± 0.50%), F3 (11.08 ± 0.46%), F4 (11.29 ± 0.39%), F5 (12.64 ± 0.41%), F6 (13.01 ± 0.44%), F7 (12.99 ± 0.29%), F8 (13.24 ± 0.19%) and F9 (13.89 ± 0.48%), which might be due to HPMC K15M concentrations. The lower percentage of moisture content in the preparations helps them to consist stable and when the completely dried film looks like a brittle film (Table 6).

Determination of drug content

The content of the drug in various primaquine-loaded transdermal preparations was found in the range of 98.09 ± 0.9–99.10 ± 1.0%, although about 100% (99.10 ± 1.0) drug content was observed in F5 primaquine-loaded transdermal film preparation (Table 6). The rug was distributed uniformly throughout the transdermal films, and the drug loss during or after the formulation of transdermal films was minimum.

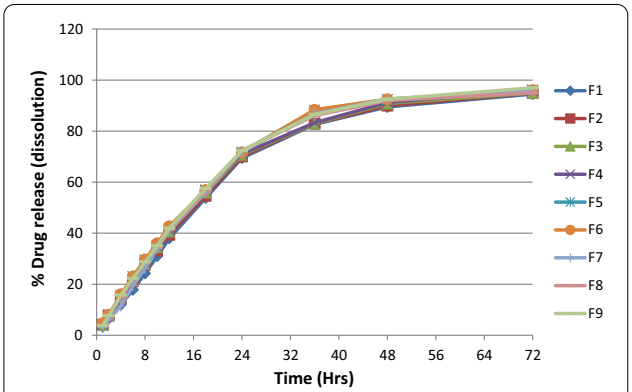

Fig. 5 % Drug release (dissolution) of formulated transdermal patch (F1–F9)

In vitro drug release from the transdermal film

The data collected from in vitro dissolution testing of the transdermal films are shown in (Fig. 5). After 1, 12, 24, 48, and 72 h of dissolution, the drug release was observed at about 4, 40, 70, 92, and 95%, respectively. So it was obvious that formulations will work for 48 h because about 92% drug was released after 48 h. The data of in vitro drug release (response 2) of the transdermal film were fitted to different models by the application of response surface methodology, and linearity was observed in the best-fitted model (Fig. 6).

Ex vivo skin permeation study

The transdermal film formulation F5 exhibited 95.91 ± 2.55% of drug permeation in 72 h (Fig. 7). When we compared the drug permeation profile at 48 h and 72 h and plotted the graph (% CDR against time) for F5 formulation, then we observed that $R^2 = 0.919$ and $R^2 = 0.833$ for 48 h and 72 h, respectively. This comparative study shows that formulation will show a good effect of up to 48 h of application. So it was clear that transdermal formulation releases the

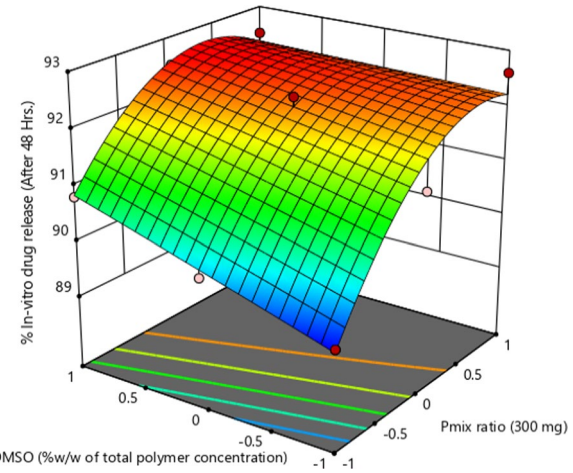

Fig. 6 Response surface plot of % in vitro of transdermal patch

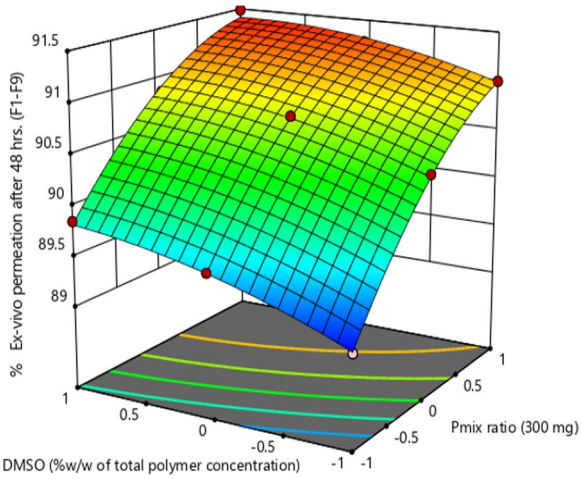

Fig. 8 Response surface plot of % ex vivo drug permeation

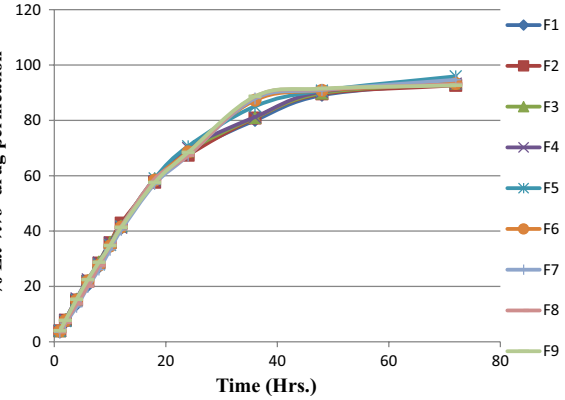

Fig. 7 Ex vivo skin drug permeation (after 72 h) of transdermal patch (F1–F9)

drug at appropriate skin flux up to 48 h and a graph of % cumulative drug concentration of drug permeation/cm^2 of the film through the abdominal skin of Wistar rat versus time showed the drug permeation might according to Zero-order kinetics as it was determined by the correlation coefficient. The data of ex vivo drug permeation (response 3) of the transdermal film were fitted to different models by the application of response surface methodology and linearity was observed in the best-fitted model (Fig. 8).

Ex vivo permeation kinetic study of the optimized film (F5) by fitting in different model

An optimized transdermal patch (F5) release kinetic mechanism was analyzed through the data fitting to the Peppas model and Higuchi's model and data compared to the correlation coefficient (R^2). The correlation coefficient (R^2) was observed as 0.9988 which was higher than other models. So it was obvious that the release of the drug from the formulation followed Zero-order release.

Statistical analysis

One-way ANOVA method was used for statistical analysis of different formulations. When the P-value ≤ 0.05, then the values of all formulations were observed significant statistically (Table 7). The model F-value implies the model was significant. Linearity was observed for all responses at ≤ 0.05 P-value. So it was obvious that the obtained data was significant.

The predicted R^2 showed reasonable agreement with the adjusted R^2, i.e. the difference was less than 0.2 (Table 8). Adequate precision measures the signal-to-noise ratio. A ratio greater than 4 was desirable. Our ratio was greater than 4, and it indicated an adequate signal.

Skin sensitivity test

The results of acute skin irritation experiments (repeated and singled exposure) are expressed in Fig. 9a, b, c, and d (Table 9). No clinical changes or sign in body weight was found in any site where transdermal films were applied. No skin response edema or erythema was observed in rabbits.

Stability study

A stability study of optimized transdermal patch formulation (F5) was conducted for three months under different temperate conditions (25 °C ± 2 °C, 40 °C ± 0.1 °C,

Table 7 ANOVA for tensile strength, % in vitro drug release, and % ex vivo skin permeation (F1–F9)

Parameters	Source	Sum of squares	DF	Mean square	*F*-value	*P*-value	
Tensile strength	Model	0.1484	5	0.0297	64.49	< 0.0001	Significant
% In vitro drug release	Model	22.02	5	4.40	54.33	< 0.0001	Significant
% ex vivo skin permeation	Model	10.08	5	2.02	940.99	< 0.0001	Significant

Table 8 Fit statistics data for tensile strength, % in vitro drug release, and % ex vivo skin permeation (F1–F9)

Parameters	SD	Mean	CV%	R^2	Adjusted R^2	Predicted R^2	Adequate Precision
Tensile strength	0.0215	0.4650	4.61	0.9699	0.9549	0.7886	22.3726
% In vitro drug release	0.2847	91.50	0.3112	0.9645	0.9467	0.8174	18.0658
% ex vivo skin permeation	0.0463	90.43	0.0512	0.9979	0.9968	0.9890	81.3877

CV Coefficient of variation, *SD* Standard deviation

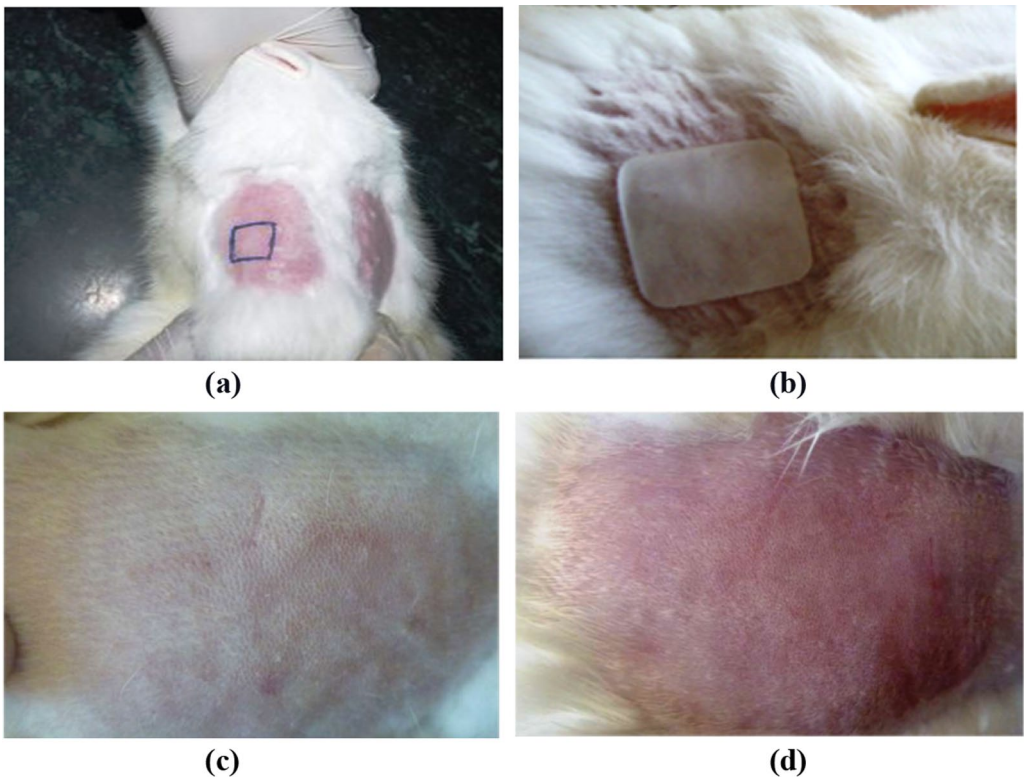

Fig. 9 **a** Preparation of patch application. **b** Patch application. **c** Single use patch after 72 h. **d** Acute repeated patch

and 4 °C ± 0.2 °C). Optimized film (F5) was stable and consistent for all evaluated parameters (Table 10).

Discussion

All the formulations of primaquine-loaded transdermal films showed a thickness range from 0.32 to 0.52 mm. The high thickness of formulation F6 and F4 was observed; it may be due to the less solubility of Eudragit RL100 in water rendering the somewhat uneven distribution of the polymer layer [25]. The low value of the standard deviation (SD) of transdermal films was indicating that the film was uniform. Average weight of 10 films for F1, F2, F3, F4, F5, F6, F7, F8 and F9 was 500, 510, 498, 502, 507, 505, 490, 501 and 504, respectively,

Table 9 Scoring for skin sensitivity test

Time of film detachment	Edema	Erythema
Acute singled skin irritation test		
1 h after detachment of film	0	0
24 h after detachment of film	0	0
48 h after detachment of film	0	0
72 h after detachment of film	0	0
Acute repeated skin irritation test		
1 h after detachment of film	0	0
24 h after detachment of film	0	0
48 h after detachment of film	0	0
72 h after detachment of film	0	0

and percentage deviations for these formulations were 4.6%, 3.92%, 3.81%, 4.18%, 4.33%, 4.36%, 4.08%, 4.79% and 4.36%, respectively. The swelling index was minimum for F4 (59.66 ± 4.3%) and maximum for F9 (79.08 ± 4.5%). The swelling index shows the hydration of patches when it was immersed in aqua. Enhanced hydration of polymers in patches leads to the creation of void spaces which may influence the sustained release profile of the matrix type of patch. The folding endurance for all factorial design films was observed as satisfactory which denotes that the films formulated using polyethylene glycol 400 in a 30% w/w of polymer concentrations were found optimum flexibility and were not brittle. Folding endurance for F1, F2, F3, F4, F5, F6, F7, F8 and F9 was 190 ± 8, 193 ± 7, 187 ± 10, 196 ± 8, 190 ± 7, 199 ± 9, 189 ± 9, 192 ± 8 and 191 ± 9. Tensile strength (Response 1) was characterized through one-way ANOVA as; the model F-value of 64.49 implies the model is significant. *P*-values were found < 0.0001and less than 0.0500 indicating model terms are significant. In vitro drug release (Response 2) was characterized through one-way ANOVA as the model F-value of 54.33 implies the model is significant. *P*-values were found < 0.0001 and less than 0.0500 indicate model terms are significant [26, 27]. Ex vivo drug permeation (Response 3) was characterized through one-way ANOVA as; the model *F*-value of 940.99 implies the model is significant. *P*-values were found < 0.0001 and less than 0.0500 indicating model terms are significant. All the data of the research were shown that it was statistically significant. When we compared the drug permeation profile at 48 h and 72 h and plotted the graph (% CDR against time) for F5 formulation then we observed that $R^2 = 0.919$ and $R^2 = 0.833$ for 48 h and 72 h, respectively. This comparative study shows that formulation will show a good effect of up to 48 h of application. When we compared our findings to the hydrogel of primaquine [28], we discovered that the hydrogel shown the release for 6–8 h, whereas the patch demonstrated the release for 48 h and in that situation, regular application of hydrogel is required; however, transdermal patches do not require frequent application.

Conclusion

The therapeutic transdermal patches of primaquine with optimum thickness, % elongation and tensile strength were formulated for transdermal application. The therapeutic transdermal patch was prepared by using Eudragit RL100: HPMC K15M (1:2) into the patch because this combination was responsible for the significant

Table 10 Stability study of optimized primaquine-loaded transdermal patch formulation (F5)

Time	Temp	% Drug content	Transparency	pH	Folding endurance (Numbers)	Tensile Strength (Kg/cm^2)	% Elongation	% Moisture content
1 Day	4 °C	99.70 ± 0.4	Y	5.4 ± 0.1	188 ± 6	0.43 ± 0.015	37.9 ± 0.12	06.75 ± 0.04
	25 °C	99.70 ± 0.0	Y	5.5 ± 0.1	190 ± 8	0.41 ± 0.014	38.6 ± 0.19	06.83 ± 0.03
	40 °C	99.70 ± 0.1	Y	5.4 ± 0.2	185 ± 6	0.42 ± 0.013	37.6 ± 0.15	06.76 ± 0.05
1 Month	4 °C	99.66 ± 0.3	Y	5.5 ± 0.1	189 ± 7	0.41 ± 0.010	37.9 ± 0.16	06.79 ± 0.06
	25 °C	99.60 ± 0.2	Y	5.4 ± 0.2	193 ± 6	0.42 ± 0.009	37.4 ± 0.10	06.71 ± 0.05
	40 °C	99.59 ± 0.2	Y	5.5 ± 0.1	191 ± 8	0.43 ± 0.014	38.5 ± 0.12	07.71 ± 0.04
2 Months	4 °C	99.53 ± 0.1	Y	5.4 ± 0.2	189 ± 9	0.42 ± 0.015	38.3 ± 0.17	07.74 ± 0.06
	25 °C	99.58 ± 0.4	Y	5.5 ± 0.1	194 ± 8	0.42 ± 0.014	38.0 ± 0.11	06.78 ± 0.05
	40 °C	99.55 ± 0.3	Y	5.4 ± 0.1	187 ± 8	0.43 ± 0.014	38.7 ± 0.15	06.73 ± 0.04
3 Months	4 °C	99.54 ± 0.2	Y	5.6 ± 0.2	186 ± 9	0.42 ± 0.015	38.1 ± 0.16	07.74 ± 0.05
	25 °C	99.54 ± 0.3	Y	5.5 ± 0.1	190 ± 8	0.42 ± 0.012	37.6 ± 0.10	07.73 ± 0.03
	40 °C	99.51 ± 0.5	Y	5.5 ± 0.1	193 ± 9	0.42 ± 0.014	38.3 ± 0.12	07.75 ± 0.04

transparent film. The permeation rate of the therapeutic transdermal patch was significant. The great permeation rate was achieved by the incorporation of dimethyl sulfoxide as a permeation enhancer. The optimized formulation was justified by using statistics. Stability studies confirmed that the therapeutic transdermal patch is a promising carrier for the delivery of primaquine.

Abbreviations

GIT: Gastrointestinal tract; DSC: Differential scanning calorimetry; FT-IR: Fourier transform infrared spectroscopy; HPMC K15M: Hydroxypropyl methylcellulose; EC: Ethylcellulose; DCM: Dichloromethane; P_{mix}: Polymer mixture; DMSO: Dimethyl sulfoxide; PEG: Polyethylene glycol; ANOVA: Analysis of variance; IAEC: Institutional Animal Ethical Committee; CPCSEA: Control for purpose of control and supervision of experiments on animals; CDR: Cumulative drug release; SD: Standard deviation; WVTR: Water vapor transmission rate; UV–VIS: Ultraviolet visible spectroscopy; PA: Physical appearance; TSFU: Transparent smooth flexible uniform; PBS: Phosphate, buffer solution; OECD: Organisation for Economic Co-operation and Development.

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Author contributions

PS designed and optimizes the study and developed the methodology. PS performed the experiments, collection and interpretation data. PS wrote the manuscript. MT contributed to manuscript revision and provided supervision. Both authors read and approved the final manuscript.

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Availability of data and materials

The datasets of research were collected from experiments and analysis of variables during current study. These datasets are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Declarations

Ethics approval and consent to participate

The ex vivo skin permeation and skin irritancy studies were completed at School of studies in pharmaceutical sciences, Jiwaji University, Gwalior, according to the protocols permitted by the Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India, under the reference no. IAEC/JU/47 on the recommendations of the Institutional Animal Ethical Committee of Jiwaji University (Gwalior, India). All animals' requirements were completed by Jiwaji University, Gwalior.

Consent for publication

The authors declare no conflict of interest.

Competing interests

The authors declare that they have no competing interests.

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