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Design and optimization of HPMC/EC-diclofenac sodium transdermal patches

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ABSTRACT

Matrix type transdermal patch of diclofenac sodium was prepared using hydroxypropylmethylcellulose (HPMC) and ethylcellulose (EC) as polymers. The preparation of patches was optimized employing 2-factor, 3-level Central Composite Design (CCD) keeping concentration of HPMC and polyethylene glycol-400 (PEG-400) as independent variables whereas drug content and drug release were set as dependent variables. The preparation of patch was characterized by FT-IR, DSC, XRD and SEM studies. The optimized batch was evaluated for drug content, *in vitro* drug release and *ex vivo* drug permeation study. *In vitro* drug release study of optimized batch revealed that 43.28% drug released in 12 hours, thus showing sustained release behaviour and followed Korsemeyer-Peppas release kinetics. However, *ex vivo* drug permeation study of optimized batch was carried out using pig ear skin displayed 20.5% drug permeated at a flux rate of 1.22 μg/cm²/h following Higuchi model of release kinetics.

Keywords: transdermal patches, diclofenac sodium, design of experiment, HPMC, ethylcellulose

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INTRODUCTION

Transdermal Drug Delivery System (TDDS) is described as independent discrete delivery system that after being placed on the intact surface of skin transports the drug(s) to the bloodstream at a limited rate through the stratum conium layer, epidermis and dermis to attain therapeutic action[1]. Oral route is the easiest approach for drug administration but it also possesses a few major limitations like poor bioavailability, poor solubility and instability in GI fluids and first pass hepatic metabolism etc. In order to defeat these limitations, there is a high demand of developing such novel drug delivery systems by which overall therapeutic effectiveness and drug safety can be enhanced. With the purpose of fulfilling such objectives and acknowledging those, TDDS was set up[2,3]. In comparison to oral route, TDDS route has several advantages such as sustained drug release, by-passing hepatic first pass metabolism, minimizing patient variability that can be given to nauseated/unconscious patients, non-invasive and self-administration and termination of treatment is possible whenever necessary[4]. A transdermal patch (skin patch) is described as a drug containing an adhesive patch which is put on the skin to achieve a specified dose of the drug via the skin into the systemic circulation[1]. There are several non-steroidal anti-inflammatory drugs incorporated into transdermal patches which have demonstrated their utilization in pharmaceuticals viz. piroxicam for treating dysmenorrhea, ketoprofen for rheumatoid arthritis, diclofenac for local muscular pain, naproxen for arthritis associated inflammation and pain[5-8]. Other NSAID drugs incorporated into transdermal patches include ibuprofen, indomethacin, loxoprofen sodium, lornoxicam, meloxicam, etc.[9-13].

Diclofenac Sodium, a Non-steroidal anti-inflammatory drug, is a derivative of phenylacetic acid and belongs to BCS-II class having low solubility and high permeability that is employed for symptomatic relief of inflammation and pain in rheumatoid arthritis, osteoarthritis, toothache, dysmenorrhea, mild to moderate muscular pains, migraines etc. Diclofenac sodium undergoes hepatic first pass metabolism due to which approx. 50% of the drug enters the bloodstream and being a NSAID, it can cause several side effects on oral administration like gastrointestinal tract irritation, ulceration of the stomach and systemic toxicity, etc. To overcome these limitations, the transdermal route is preferred for the delivery of diclofenac sodium by transdermal route. Due to very short half-life (1.5-2 hours), poor bioavailability (40-50%) and small dose (25-50 mg), diclofenac sodium can be a good candidate for transdermal drug delivery[14,15]. The diclofenac sodium patches were also explored by researchers[16,17]. A cohort of researchers developed a transdermal patch of piroxicam utilizing HPMC and EC as polymers, discovering that formulation

F1, which had a 3:1 ratio of hydrophilic to lipophilic polymers, exhibited the highest drug release and permeation for an extended duration of up to 12 hours[5]. Researchers developed a transdermal patch with piroxicam utilizing HPMC and EC as polymers, revealing that patches formulated with 2:8 and 8:2 ratios of ethyl cellulose to hydroxypropyl methyl cellulose exhibited the highest and lowest *in vitro* release of naproxen, respectively[18].

In the current research work, hydrophilic polymer HPMC is incorporated to enhance the drug release rate, resulting in pore formation upon interaction with aqueous solutions, hence facilitating drug release. EC is incorporated and it is a non-allergenic, harmless hydrophobic polymer that has excellent film-forming capabilities[19,20]. PEG-400 is utilized as a plasticizer in transdermal patch films. It intervenes among polymer chains, diminishing brittleness and enhancing flexibility, elasticity, and folding durability[21]. Castor oil functions as a permeation enhancer in the transdermal patches, augmenting the quantity of medication that permeates the stratum corneum by altering the lipid matrix composition of the skin[22]. The objective of the current work was to develop and optimize the transdermal patches using HPMC and EC as polymers containing diclofenac sodium as a model drug for sustaining the drug release. Diclofenac sodium-loaded transdermal patches were prepared by a simple and reproducible solvent casting technique using castor oil as a penetration enhancer.

The preparation of transdermal patches was optimized by 2-factor 3-level Central Composite Design (Design Expert® software Version 11.0., Stat-Ease, Inc., Minneapolis, Minnesota, USA) and was carried out as per the suggested design protocol. The effect of formulation variables such as concentration of HPMC (X_1) and concentration of PEG-400 (X_2) on drug content (Y_1) and drug release (Y_2) of transdermal patches was studied using CCD to prepare an optimized batch of optimal drug content and release. The optimized batch was characterized by Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD) and Scanning Electron Microscopy (SEM). The optimized batch was further evaluated for *in vitro* drug release and *ex vivo* permeation and deposition studies using isolated pig ear skin by employing Franz diffusion cell.

METHODOLOGY

Materials

Diclofenac sodium was gifted by Arbro Pharmaceuticals Pvt. Ltd. (New Delhi, India). HPMC E5, PEG-400 and castor oil were purchased from High Purity Laboratory Chemicals (HPLC) Pvt. Ltd. (Mumbai, India). Ethyl cellulose, methanol and dichloromethane were procured from SD Fine Chemical Ltd. (India). All other chemical reagents used were of analytical grade.

Preparation of transdermal patches

The matrix-type transdermal patches of diclofenac sodium were prepared by the solvent casting technique with slight modifications in the method as reported earlier[23,24].

For the preparation of patch, accurately weighed desired polymers, i.e., ethylcellulose (2.5%) and different concentrations of HPMC (2.5%, 3.75% and 5%) were mixed in 10 ml of solvent composed of methanol and dichloromethane (1:1). Drug (1% w/v) was added to the above polymer solution and mixed thoroughly by continuously stirring the mixture for 60 minutes on a magnetic stirrer to get a homogenous mixture. The different concentrations of PEG-400 (1%, 3% and 5%) as plasticizer were transferred to the above solution containing 2% w/v of castor oil as penetration enhancer. The Polyvinyl Alcohol (PVA) backing layer was prepared by pouring 4% w/v of PVA solution on petri plates and then subjected to drying at 60°C for 6 hours. A transparent backing layer was obtained after drying process and was placed evenly on the petri dish on which the polymer solution was poured. To control the evaporation rate of the solvent, an inverted funnel was mounted on the petriplate and the solvent mixture was evaporated at room temperature for 24 hours. The patch has been removed after 24 hours and was placed between the aluminum foil to protect it from the outer environment and stored in desiccators for further use.

Experimental design

HPMC is a hydrophilic polymer that absorbs moisture, swelling to create a gel-like matrix that facilitates medication diffusion and release. Its viscosity and capacity to absorb water render it optimal for regulating the medication release rate and enhancing patch flexibility[21,25]. PEG-400 is a widely utilized plasticizer in transdermal patches; it boosts flexibility, diminishes brittleness, and improves the mechanical strength of the patch film. In addition to plasticization, PEG-400 can influence water absorption and the mobility of polymer chains within the film matrix. Elevated PEG-400 levels generally improve hydration and diffusivity, potentially augmenting medication release rates and altering permeation characteristics[26].

The concentration of HPMC (X_1) directly influences matrix formation, release rate, mechanical strength, and drug diffusion properties. The concentration of PEG-400 (X_2) affects the flexibility of the matrix, the degree of plasticization, and the diffusion routes within the polymer, thereby altering dependent reactions such as cumulative drug release permeation flow. Ethylcellulose, conversely, is a hydrophobic, water-insoluble polymer that creates a stiffer matrix. It impedes medication release owing to its restricted interaction with water[27].

The preparation of diclofenac sodium-loaded transdermal patches was optimized with design of experiment (DoE) software using a two-factor, three-level central composite design (CCD) and selecting α=1 as per the standard protocol. On the basis of preliminary trials, the concentration of HPMC (X_1) and PEG-400 (X_2) were selected as formulation independent variables. Drug content % (Y_1) and drug release % (Y_2) were taken as dependent variables. All other variables were kept unaltered throughout the study[13]. Experimental runs suggested by the design expert software were prepared having 4 axial points, 4 factorial points and 5 replicates of the center point to improve the reproducibility of the method (Table 1). The experimental design and statistical analysis of the obtained data (ANOVA) was performed as per the design protocol by using Design Expert® software.

Table 1. Evaluation of different batches of diclofenac sodium-loaded transdermal patches prepared as per Central Composite Design

Experiment No.	Conc. of HPMC (X_1)	Conc. of PEG-400 (X_2)	Drug Content (Y_1) ± SD	Drug Release (Y_2) ± SD
	(% w/v)	(% w/v)	(%)	(%) in 12 hours
1	5	1	94.66 ± 0.01	44.04 ± 0.01
2	5	5	99.47 ± 0.01	54.76 ± 0.2
3	2.5	3	93.7 ± 0.18	42.09 ± 0.19
4	3.75	5	99.47 ± 0.003	52.9 ± 0.01
5	3.75	3	93.22 ± 0.26	42.98 ± 0.093
6	3.75	3	99.95 ± 0.02	55.79 ± 0.113
7	3.75	3	96.1 ± 0.17	52.46 ± 0.02
8	3.75	3	96.58 ± 0.36	49.39 ± 0.022
9	3.75	1	97.06 ± 0.01	46.98 ± 0.065
10	2.5	5	96.1 ± 0.09	47.35 ± 0.01
11	3.75	3	97.06 ± 0.14	49.36 ± 0.09
12	5	3	96.58 ± 0.14	47.28 ± 0.011
13	2.5	1	97.06 ± 0.02	47.35 ± 0.006

Characterization

Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra of diclofenac sodium and optimized batch were analyzed in range between 4000-400 cm^{-1} by using FTIR spectrophotometer (Perkin Elmer Spectrum, BX II), employing KBr pellet technique[28].

Differential scanning calorimetry (DSC)

DSC thermogram of diclofenac sodium and an optimized batch of transdermal patch was acquired by using DSC analyzer (Q-10, TA Instruments Waters). In this analysis, a few mg of the drug sample was kept in DSC pan which was sealed hermetically. The sample was heated in DSC equipment under liquid nitrogen condition at a constant rate of 10°C per minute over a temperature range of 20-300°C[29].

X-ray diffraction (XRD)

X-ray diffraction analysis of an optimized batch of transdermal patch and pure drug was carried out utilizing an X-ray diffractometer [Tabletop (Miniflex-II) Japan]. Samples were irradiated with monochromatized Cu-Kα radiation and investigated between 10° to 70° diffraction angle (2θ) range with a speed of scanning 0.05 $min.^{-1}$ at room temperature[30].

Scanning electron microscopy

SEM was used to examine the morphological characteristics of the optimized transdermal patch (7610F Plus/JEOL). The sample after coating with gold was placed on the sample holder employing double adhesive carbon tape. The photomicrographs were recorded at different magnifications having an accelerating voltage of 20kV[31].

Evaluation of transdermal patches

Physical appearance

All formulated transdermal patches were manually investigated for their color, clarity, air bubble entrapment, smoothness, flexibility and texture that significantly influences the patient's acceptance for the patch and its therapeutic action[32].

Weight variation

The prepared transdermal patches were cut into 4 cm^2 and three patches were randomly picked and weighed using a digital balance. The average weight of three with a standard deviation was measured for all batches. This test was

performed to study the weight uniformity and thus determine the batch-to-batch weight variation. The test was performed in triplicate[4].

Thickness

A digital Vernier Caliper was utilized to measure the thickness of the transdermal patches. The patches were cut into 4 cm^2 cm and thickness was estimated at four several points. The average of four observations with the standard deviation was calculated. Thickness was measured in triplicate (n=3)[33].

Folding endurance

Folding endurance of the prepared transdermal patch was measured by taking a smallpiece of the patch 4 cm^2 and then repeatedly folding it at the same place until it broke. Folding endurance was calculated as the number of times the transdermal patch could be folded at the same place without breaking. The test was done in triplicate (n=3). Likewise, folding endurance of all batches was calculated[34].

% moisture content

To determine the % moisture present, pre-weighed different patches (4 cm^2) were placed in desiccators containing calcium chloride as desiccant for 24 hours followed by weighing of all the patches till constant weight was observed. The study was performed in triplicate. Moisture content (%) was determined by the following formula[35].

$$\% \text{ Moisture Content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \text{ X } 100 \quad \text{[Eq 1]}$$

% moisture uptake

The developed patches were weighed and put in desiccators at normal room temperature in saturated solution of potassium chloride for 3 days in order to maintain 84% relative humidity to gain the moisture. The patches were weighed again after 3 days or until a constant weight was obtained. The test was performed in triplicate. By using the following formula, uptake of moisture (%) was determined[32].

$$\% \text{ Moisture Uptake} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \text{ X } 100 \quad \text{[Eq 2]}$$

Drug content (%)

The estimation of drug content was carried out by dissolving patches of specific area 4 cm^2 in a volumetric flask (10 ml) containing casting solvent (methanol) that were sonicated at 37 ± 0.5°C for 1 hour followed by filtration using Whatman filter paper. The drug content was estimated by taking the absorbance after suitable dilution at λmax 276 nm using UV-Vis spectrophotometer[36]. The test was done in triplicate (n=3).

***In vitro* drug release study**

The release of diclofenac sodium from the prepared patches was analyzed by employing a Franz diffusion cell possessing a receptor chamber of 100 ml capacity with exposed surface area of 4.9 cm^2. The dialysis membrane taken as semi-permeable membrane for diffusion was kept in the middle of donor and receptor chamber of Franz diffusion cell. The transdermal patch was mounted over the dialysis membrane and securely clamped between donor and receptor chamber. The receptor chamber filled with phosphate buffer solution (pH 6.8) was stirred at 35-45 rpm at a temperature 37 ± 0.5°C. An aliquot (3 ml) was taken at specified intervals of time for 12 hours and replaced with equal volume of receptor medium to maintain the sink conditions. The study was performed in triplicate. The amount of drug release was spectrophotometrically estimated by measuring the absorbance at λ_{max} of 276 nm[37,38].

***Ex vivo* permeation and deposition study**

The *ex vivo* permeation and deposition of diclofenac sodium from the optimized patch was studied by using a Franz diffusion cell with a receptor chamber capacity of 100 ml and exposed surface area 4.9 cm^2. Hairless pig ear skin was a model skin for permeation study. The receptor chamber was filled with phosphate buffer solution (pH 6.8), thermostated at 37 ± 0.5°C and constantly stirred on a magnetic stirrer. The skin sample was placed over the receptor chamber facing the stratum corneum towards the donor chamber. The same-sized patch was mounted on the skin sample and then safely clamped in between the donor and receptor chamber. The samples (3 ml) were taken at specified intervals of time for 6 hours from the receptor chamber and replaced with an equal volume of receptor medium to maintain the sink conditions. To measure the amount of diclofenac sodium permeated, the absorbance of the samples was measured at λ_{max} of 276 nm by a UV-Vis spectrophotometer[36,39].

On completion of the study, the tissue was detached from the diffusion cell to determine the quantity of drug deposited in the skin layer. Skin samples were thoroughly washed with distilled water and normal saline solution. The drug

retained in the skin was extracted by homogenizing the tissue in methanol and the dispersion so retrieved was filtered with a 0.22-mm membrane filter. The processed sample after suitable dilution was analyzed by a validated UV-Vis method[40].

Data and statistical analysis

The data obtained from *ex vivo* drug permeation study was used for the estimation of steady state flux (Jss), permeability coefficient (Kp) and permeation rate by calculating the cumulative amount of drug permeated per unit area (μg/cm²) of pig ear skin that was plotted against the function of time (h). The steady state flux (Jss) was calculated from the slope of a linear plot of cumulative drug permeation per unit area (μg/cm²) as a function of time (h) using linear regression analysis. The permeability coefficient (Kp) was calculated by dividing the flux (Jss) with the initial concentration of drug present in the donor compartment. The permeation rate was calculated from the slope of the graph plotted between cumulative amount of drug permeated per unit area (μg/cm²) as a function of the square of time[40,41]. All experiments were performed in triplicate, and the results are expressed as mean ± standard deviation (SD). All calculations, graphical analysis, and regression analysis were performed using Microsoft Excel (Microsoft Corporation, USA).

RESULTS and DISCUSSION

Preparation of transdermal patches

Preparation of transdermal patches is achieved by the solvent casting method, employing face-centered, central composite design (CCD) to optimize the formulation of transdermal patches. The concentration of HPMC (X_1) and PEG-400 (X_2) were selected as 2.5-5% and 1-3%, respectively. The results of drug content (Y_1) and drug release (Y_2) of different batches of diclofenac sodium loaded transdermal batches were prepared as per the design protocol of CCD and are shown in Table 1.

Characterization

Fourier transform infrared spectroscopy analysis

Figure 1 represents the FTIR spectra of diclofenac sodium, the physical mixture and the optimized batch of the transdermal patch. FTIR spectrogram of diclofenac sodium showed the appearance of definite peaks at 3233.10 cm^{-1} due to the existence of aromatic secondary amine group, at 1398.03 cm^{-1} due the presence of metallic salt of Na^+, at 747.97 cm^{-1} due to the aromatic -C-Cl bond, at 840.47 cm^{-1} due to the out of plane (oop) -C-H bending and at 952.54

cm^{-1} due to the presence of in plane -C-H bending. FTIR spectra of the physical mixture showed characteristic peaks at 3460.11, 2932.39, 1639.41, 1604.6, 1577.84, 1453.39 cm^{-1} corresponding to stretching of aromatic secondary amine (-N-H), methyl (-C-H) stretching, carbonyl (-C=O) stretching, aromatic (-C-C) stretching, aromatic ring stretching and presence of metallic salts of Na+, respectively. The definite peaks at 950.84 cm^{-1} and 839.36 cm^{-1}due to the presence of in plane -C-H bending and oop-C-H bending, respectively, also appeared whereas peaks appearing at 748.64 cm^{-1} and 615.45 cm^{-1} may be ascribed to aromatic -C-Cl and oop-OH bending, respectively. The IR spectrum of the optimized batch exhibits an absorption peak at 3451.62 cm^{-1} that may be ascribed to aromatic -N-H stretching while peaks appearing at 2928.88, 1639.63, 1578.22 and 1454.21 cm^{-1} may be due to methyl (-C-H) stretching, carbonyl (-C=O) stretching, aromatic (-C-C) stretching, aromatic ring stretching and presence of metallic salts of Na+, respectively. The peaks at 949.05, 885.24 and 580.37 cm^{-1} may be attributed to in plane -C-H bending, oop-C-H bending and oop-OH bending, respectively. However, comparison of the FTIR spectra showed absence of new characteristic peaks in the optimized batch indicating that there are no physical and chemical interactions between diclofenac sodium and excipients.

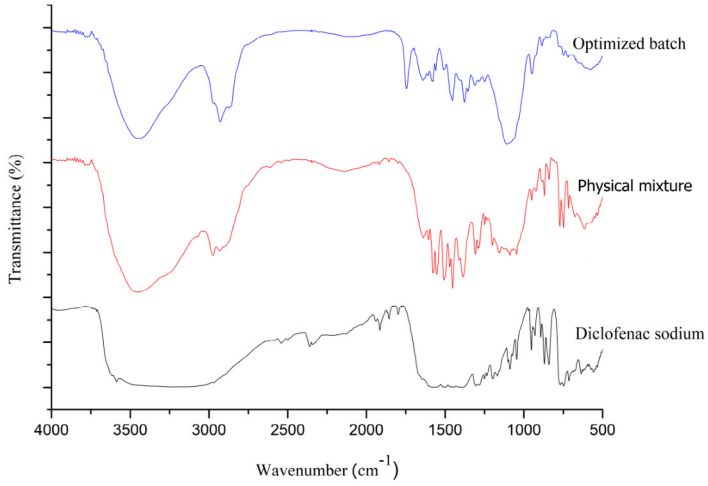


Figure 1. FTIR Spectrum of diclofenac sodium, physical mixture and optimized batch

Differential scanning calorimetry

Figure 2 exhibits the DSC thermogram of diclofenac sodium and the optimized batch of the transdermal patch. The DSC thermogram of pure drug demonstrated the sharp melting endothermic peak that stretches from 270°C to 280°C along with a maximum peak at 276°C, equivalent to the melting endothermic range of pure diclofenac sodium. The DSC thermogram of the optimized batch shows two broad endotherms at 57.48°C and 112.28°C with heat of fusion of 4.48 J/g and 12.55 J/g, respectively and two dominant endotherms at 93.50°C and 255.71°C with heat of fusion of 19.12 J/g and 13.58 J/g, respectively corresponding to moisture loss and melting point of drug. Thus, the shifting of endotherm, appearance of new endotherms and changes in heat of fusion indicate that modifications of diclofenac sodium have occurred.

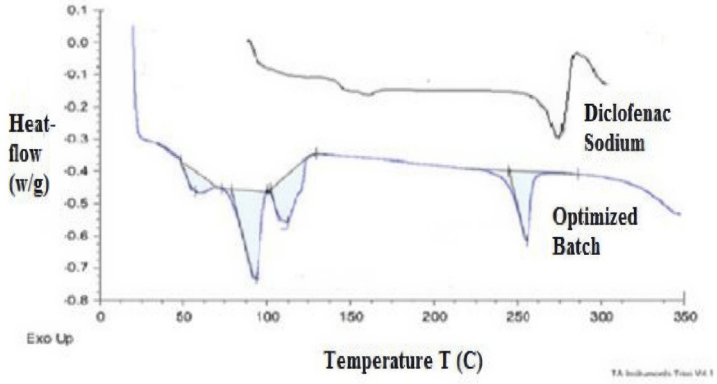


Figure 2. DSC thermogram of diclofenac sodium and optimized batch

X-ray diffraction

XRD analysis was carried out to verify the physical and chemical characteristics of drug and the optimized matrix transdermal patch. X-ray diffraction spectra of drug and the optimized formulation are shown in Figure 3. The XRD spectrum of pure diclofenac sodium showed several sharp intense peaks at 13.48, 14.52, 18.68, 20.34, 21.16, 24.06, 26.1, 32.2, 36.5 (2θ), which indicated the crystalline nature of pure drug. X-ray diffraction spectra of the optimized formulation showed typical amorphous spectra for materials. Thereby revealing that the drug has been incorporated in an amorphous polymeric matrix.

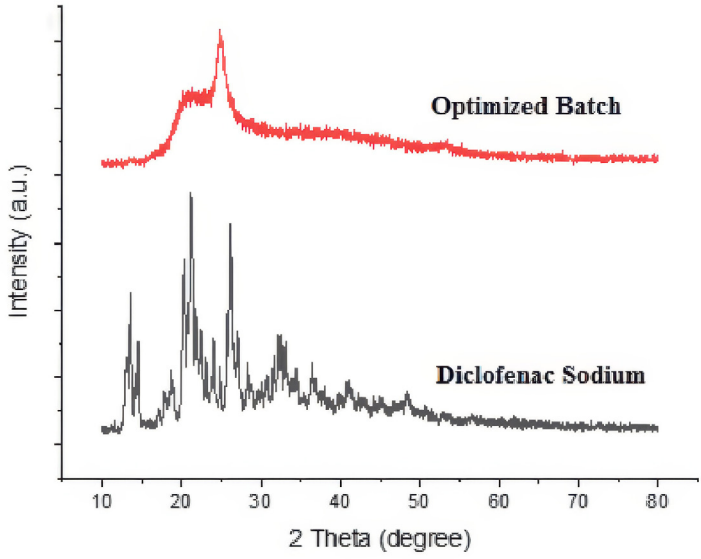


Figure 3. XRD spectra of diclofenac sodium and optimized batch of transdermal patch

Scanning electron microscopy

SEM analysis of optimized based showed that particles of formulation were approximately spherical in shape as shown below Figure 4. The scanning electron microscopy analysis of the optimized batch exhibited that the drug was available in the polymeric matrix patch. The drug was uniformly distributed and homogenous in nature.

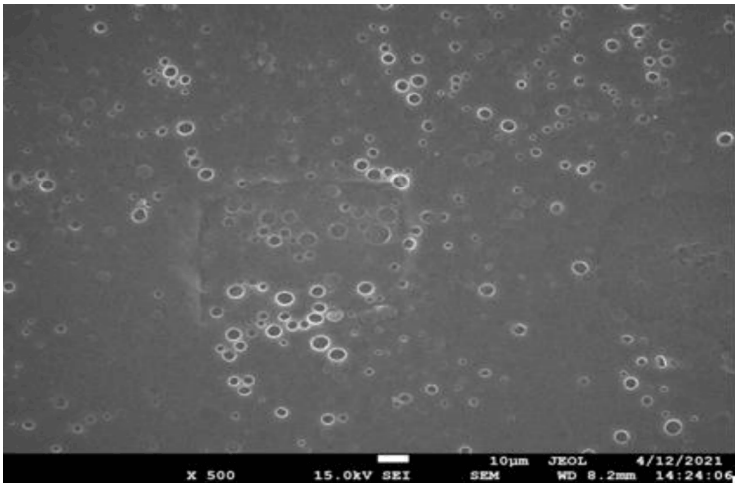


Figure 4. SEM image of optimized batch of transdermal patch

Experimental design

Central Composite Design – Response Surface Method was used to analyze the effect of two independent factors, i.e., concentration of HPMC and PEG-400 (X_1 and X_2) on response factors drug content and drug release (Y_1 and Y_2). CCD helps to analyze the high number of factors at various levels with a limited number of experiments and develops a model without having to look at all of the points in a full factorial design. The obtained data was examined and fitted into different polynomial models to choose the best-fit model for independent and dependent factors. It was examined that the responses Y_1 (% drug content) and Y_2 (% drug release) fitted best into linear response surface model. In order to find the best value of the independent variables, the obtained experimental data was statistically analyzed for achieving objective of the study.

The results of ANOVA test on linear response surface model reported in Table 2, showed that the model was significant having non-significant lack of fit. The signal to noise ratio as determined by adequate precision was found to be and 25.521 for Y_1 and 19.288 for Y_2, reveals an adequate signal and the model can be utilized to navigate the design space.

Drug content and drug release

In the present study, it was observed that transdermal patches were developed with desired drug content (Y_1), lies in the range of 93.22-99.47% (Table 1). For drug content (%), a linear model having F-value 106.81 was observed to be significant with p-value of <0.0001. The coefficient of determination (R^2) measures the total variability described by the model, and was found to be 0.9553, demonstrating that linear model can describe 95% variability in the response factor and the remaining 5% variability is due to the noise. The higher the value of R^2, the stronger will be the correlation between experimental and predicted values. The actual value of R^2 was greater than the adjusted value of R^2, i.e., 0.9463, indicating the present linear model's suitability. The polynomial equation that shows relation between independent variables and drug content (%) is displayed in Equation 3. The positive coefficient of X_1 exhibits that drug content (%) pronouncedly (<0.0001)) increases with increase in concentration of HPMC indicating synergistic effect. Contrarily, the negative coefficient of X_2 exhibits that drug content (%) pronouncedly (0.6939) decreases with increase in concentration of PEG-400, indicating antagonistic effect. The three-dimensional (3-D) response surface plots (Figure 5 a) show that increase in concentration of HPMC results in an increase in drug content (%) and PEG-400 have no significant on drug content.

$$Y1 = +96.69 + 2.88A - 0.0800B \quad [Eq\ 3]$$

The second response studied on transdermal patches is % drug release (Y_2). It was observed that transdermal patches were developed with desired sustained drug release, lies in the range of 42.09-55.79% in 12 hours (Table 1). For drug release (%), a linear model having an F-value 46.49 was observed to be significant with a p-value of <0.0001. The coefficient of determination (R^2) measures the total variability described by the model, and was found to be 0.9029, demonstrating that linear model can describe 90% variability in the response factor and remaining 10% variability is due to the noise. The higher the value of R^2, the stronger will be the correlation between experimental and predicted values. The actual value of R^2 was greater than the adjusted value of R^2, i.e., 0.8835, indicating the present linear model's suitability. The polynomial equation that shows the relation between independent variables and drug release (%) is displayed in Equation 4. The positive coefficient of X_1 exhibits that drug release (%) pronouncedly (<0.0001) increases with an increase in concentration of HPMC indicating a synergistic effect. Contrarily, the negative coefficient of X_2 exhibits that drug release (%) pronouncedly (0.0875) decreases with increase in concentration of PEG-400 indicating antagonistic effect. The three-dimensional (3-D) response surface plots (Figure 5[b]) shows that increase in concentration of HPMC results in an increase in drug release (%) and PEG-400 have no significant effect on drug release.

$$Y2 = +48.67 + 5.72A - 1.15B \quad [Eq\ 4]$$

Table 2. Results of regression analysis of variance (ANOVA) for drug content and drug release and F and p values of both responses

Response Factors						**Lack of Fit**	
	F-value	**Prob>F-value**	**R^2**	**Adjusted R^2**	**Adequate**	**F-value**	**Prob>F-value**
					Precision		
Y_1	106.81	<0.0001	0.9553	0.9463	25.521	1.45	0.3751
Y_2	46.49	<0.0001	0.9029	0.8835	19.288	3.31	0.1335
Parameter			**Y_1, Drug Content (%)**		**Y_2, Drug Release (%)**		
			F-value	**F-value**	**F-value**	**F-value**	
X_1			213.46	<0.0001	89.38	<0.0001	
X_2			0.1641	0.6939	3.59	0.0875	

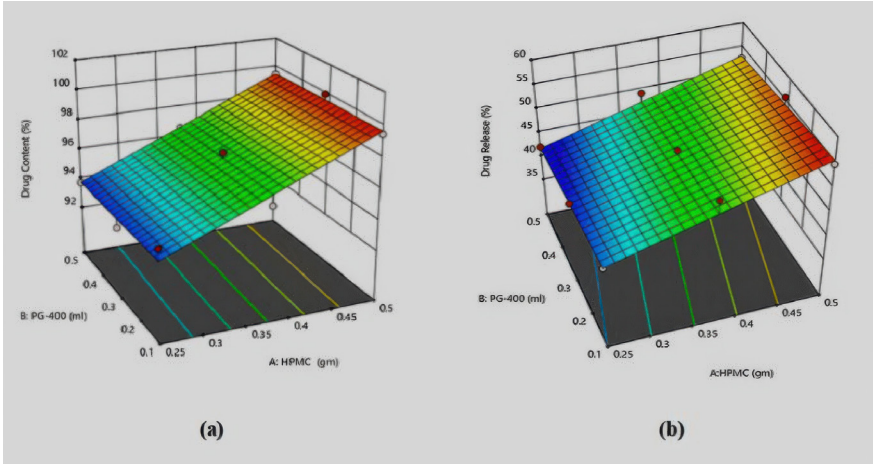


Figure 5. (a, b) Response surface plots showing the effect of concentration of HPMC and PEG-400 on drug content (Y_1) and drug release (Y_2).

A numerical optimization tool of Design Expert® software (v.11.0) was used to prepare an optimized batch employing the desirability approach having desired responses with constraints for maximum drug content (Y_1) and minimum drug release (Y_2) as the goals to find out the optimal concentration of independent factors in the optimized batch. The optimization tool provided various sets of possible solutions. The optimum suggested values of concentration of HPMC and PEG-400 with the highest desirability were 2.54% and 4.85%, respectively (batch 3). Using these concentrations, an optimized batch of diclofenac sodium loaded transdermal patch was prepared and showed that drug content was 94.44% (predicted 93.834) and drug release was 43.28% (predicted 42.087). The predicted and observed values are in closer agreement indicating that the polynomial model has a high predictive ability and are suitable for the preparation of diclofenac sodium loaded transdermal patches with desired drug content and drug release.

Physicochemical characterization of diclofenac sodium loaded transdermal patches

The prepared 13 batches of transdermal patches were analyzed further for their physiochemical parameters (Table 3) like physical appearance, uniformity of weight, thickness, folding endurance, % moisture content, % moisture absorption, drug content (%) and drug release (%) and all results are reported as mean ± standard deviation (SD). All 13 batches of prepared transdermal patches were observed to be clear, transparent, uniform, smooth, flexible and free from air bubble entrapment. Drug content estimation was of

great importance for predicting homogenous and accurate distribution of drug in the formulation. The result of drug content (%) of 13 batches varies from 93.22% to 99.95% and results showed the homogenous dispersion of drug in the formulated patches. Drug release (%) of 13 batches lies in range of 42.09 to 54.76% showed sustained release of drug. The results demonstrated that as we increase the HPMC concentration, % drug release also increases.

Table 3. Physicochemical evaluation of diclofenac sodium transdermal patches

Sr. No.	Weight Variation ± SD (gm)	Thickness ± SD (mm)	Folding Endurance ± SD	Moisture Content ± SD (%)	Moisture Uptake ± SD (%)	Drug Content ± SD (%)	Drug Release ± SD (%)
F1	0.119 ± 0	0.21 ± 0.006	245 ± 1.5	2.19 ± 0.012	1.85 ± 0.017	94.66 ± 0.01	44.04 ± 0.01
F2	0.124 ± 0.0005	0.238 ± 0.003	241 ± 2.5	4.08 ± 0.015	3.20 ± 0.014	99.47 ± 0.01	54.76 ± 0.2
F3	0.149 ± 0.001	0.213 ± 0.014	247 ± 3.6	2.14 ± 0.009	1.73 ± 0.191	93.7 ± 0.18	42.09 ± 0.19
F4	0.232 ± 0.006	0.371 ± 0.009	244 ± 3	5.22 ± 0.019	3.63 ± 0.022	99.47 ± 0.003	52.9 ± 0.01
F5	0.167 ± 0.001	0.265 ± 0.006	240 ± 1	2.48 ± 0.012	1.99 ± 0.051	93.22 ± 0.26	42.98 ± 0.093
F6	0.187 ± 0.002	0.334 ± 0.006	242 ± 4	4.76 ± 0.030	3.29 ± 0.033	99.95 ± 0.02	55.79 ± 0.113
F7	0.124 ± 0.124	0.239 ± 0.007	250 ± 1.5	3.43 ± 0.016	2.97 ± 0.091	96.1 ± 0.17	52.46 ± 0.02
F8	0.153 ± 0.0005	0.235 ± 0.007	249 ± 2.6	3.69 ± 0.125	2.66 ± 0.391	96.58 ± 0.36	49.39 ± 0.022
F9	0.122 ± 0.001	0.259 ± 0.005	245 ± 4.5	3.60 ± 0.020	2.42 ± 0.308	97.06 ± 0.01	46.98 ± 0.065
F10	0.124 ± 0.0010.	0.246 ± 0.006	240 ± 2	3.18 ± 0.019	2.68 ± 0.362	96.1 ± 0.09	47.35 ± 0.01
F11	0.199 ± 0.001	0.246 ± 0.006	240 ± 2	3.72 ± 0.019	2.45 ± 0.68	97.06 ± 0.14	49.36 ± 0.09
F12	0.122 ± 0.001	0.249 ± 0.007	249 ± 2	3.24 ± 0.027	2.48 ± 0.380	96.58 ± 0.14	47.28 ± 0.011
F13	0.116 ± 0.001	0.247 ± 0.008	244 ± 1.5	3.22 ± 0.026	2.52 ± 0.361	97.06 ± 0.02	47.35 ± 0.006

Characterization of optimized batch

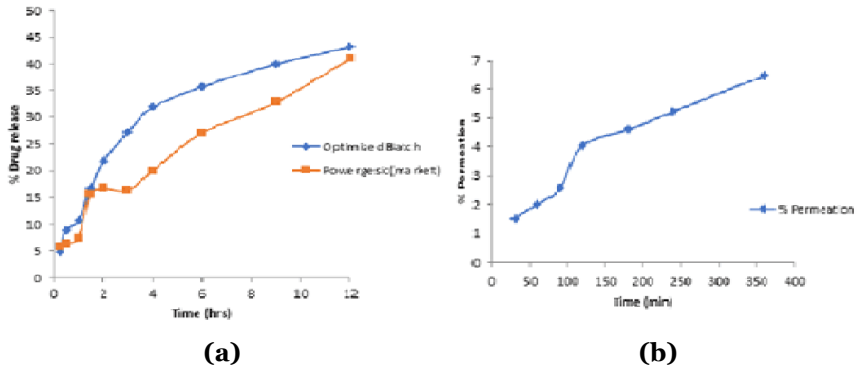
Drug content (%)

The result of drug content (%) of optimized batch was calculated and found to be 94.44%. The predicted value of drug content (%) given by CCD was found to be 93.834%. Hence, it is concluded that the drug diclofenac sodium was loaded successfully in the transdermal patches.

In vitro drug release study

The *in vitro* release of diclofenac sodium from optimized batch of transdermal patch was evaluated by Franz diffusion cell in phosphate buffer (pH 6.8) at 37 ± 0.5°C and compared with the *in vitro* release of Powergesic (marketed patch containing diclofenac 100 mg and manufactured by Jenburkt Pharmaceuticals

Ltd) as shown in Figure 6 (a). The release profile of optimized batch shows comparable drug release about 43.28% over specified time period of 12 hours as compared to powergesic that demonstrates about 41.30% release in 12 hours. To analyze the release kinetics and mechanism of drug release, the obtained data were fitted into different kinetic models like zero order, first order, Higuchi plot and Korsmeyer-Peppas plot. The regression coefficient (R^2) was calculated for all models. The R^2 value of zero order, first order, Higuchi plot and Korsmeyer-Peppas plot was found to be 0.782, 0.828, 0.900 and 0.913, respectively for optimized batch and 0.971, 0.957, 0.974 and 0.949, respectively for Powergesic. It was observed that drug release of the optimized batch follows Korsemeyer-Peppas plot kinetics (R^2=0.913) and drug release of Powergesic follows Higuchi square root kinetics (R^2=0.974). Further, the release exponent (n) was calculated from the Korsemeyer-Peppas plot and found to be 0.594 and 0.532 (n>0.5) for optimized batch and Powergesic, respectively, which indicates the release of diclofenac occurs through a non-Fickian diffusion mechanism.



(a) **(b)**

Figure 6. (a) Comparison between Drug Release Profile of Optimized Batch and Powergesic (marketed patch); (b) % Permeation study of optimized batch across pig ear skin

Ex vivo drug permeation and deposition study

The *ex vivo* permeation study was done on pig ear skin for optimized batch of transdermal patch. Figure 6 (b) shows the % cumulative of drug permeated from the optimized batch in 6 hours. After performing the *ex vivo* permeation study, the optimized formulation was subjected to data analysis and obtained data is summarized in Table 4. The study demonstrated that 20.5% drug is permeated through pig ear skin in 6 hours. The steady-state flux and permeability coefficient (Kp) were found to be 1.221 μg/cm^2/h and 0.0002 cm/h respectively. The permeation rate was found to be 30.90 μg/cm^2/h$^{1/2}$.

Table 4. Permeation of diclofenac sodium transdermal patch formulation

Time (min)	Amt. of Drug Penetrated (mg)	%Permeation
30	0.12	1.52
60	0.16	1.99
90	0.21	2.56
120	0.32	4.04
180	0.36	4.59
240	0.42	5.22
360	0.52	6.49
	Amt. of Drug Deposited (mg)	**%Deposition**
After 360 min	1.12	14.01
Total % (skin permeation + deposition)		20.5

To analyze the permeation kinetics and mechanism of drug permeation, the obtained data were fitted into different kinetic models like zero order, first order, Higuchi plot and Korsemeyer-Peppas plot and regression coefficient (R^2) was calculated for all models. The R^2 value of zero order, first order, Higuchi plot and Korsemeyer-Peppas plot was found to be 0.934, 0.937, 0.972 and 0.966 respectively. Thus, the drug permeation of optimized batch follows Higuchi plot kinetics (R^2=0.972). Further, the release exponent (n) was calculated from Korsemeyer-Peppas plot and found to be 0.622 (n>0.5) which indicates the permeation of diclofenac occurs through Non-Fickian diffusion mechanism.

In the current research work, diclofenac sodium-loaded transdermal patches were successfully prepared using the solvent casting technique and optimized using a two-factor, three-level Central Composite Design (CCD). The CCD was employed to investigate the effects of the critical formulation variables on the quality attributes of the final transdermal formulation. The optimized transdermal patch formulation was obtained using the numerical optimization tool of the CCD and was found to be similar to experimental Batch 3. The optimized formulation was characterized by FTIR, DSC, and XRD analyses, which confirmed the absence of any significant interaction between the drug and the excipients. SEM analysis of the optimized formulation demonstrated that

the drug was uniformly distributed throughout the patch and exhibited a non-porous morphology with spherical characteristics. The optimized transdermal patch exhibited 43.28% release of diclofenac sodium over a period of 12 hours and followed the Korsmeyer-Peppas release kinetics model, indicating a non-Fickian mechanism of drug release. The *ex vivo* drug permeation study of the optimized formulation showed that 20.5% of the drug permeated through pig ear skin within 6 hours and followed the Higuchi kinetic model, indicating a non-Fickian diffusion mechanism. These findings demonstrate that the optimization of diclofenac sodium-loaded transdermal patches using the CCD approach provides comprehensive information on formulation characteristics and variable interactions while reducing the number of experimental trials required. Furthermore, the CCD model proved to be an effective and reliable tool for predicting the physicochemical properties of transdermal patches. Therefore, the transdermal patches developed in the present study may serve as a promising alternative to the oral administration of diclofenac sodium, with the potential to minimize oral side effects while providing sustained drug release over an extended period.

STATEMENT OF ETHICS

This study does not require any ethical permission.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

AS: Research, conceptualization, data collection and writing original draft; MB and KB: Supervision, writing-reviewing, editing, and data collection; AK: reviewing and editing.

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