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Original Article

Optimization and Characterization of Lisinopril Loaded Transdermal Patches by Using Factorial Design

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ABSTRACT

Background and Objectives: This study aimed for systemic and sustained delivery of drug via non-parental route. **Materials and Methods:** Transdermal patches were prepared by using solvent evaporation method and optimized using 2-factor, 3-level design to investigate the influence of Ethyl Cellulose and HPMC on their tensile strength and drug release. **Results:** Optimized transdermal patches have shown uniform drug distribution with tensile strength 3.54±0.40 kg/mm^2 and *in vitro* release 94.41±8.7%. The drug content was found to be between 93.84% and 99.62%, indicating a uniform distribution of medication. They were discovered to have a fairly satisfactory moisture content and moisture uptake, which aids in their ability to stay dry and stable. Every formulation underwent an *in vitro* drug release investigation, and the results showed that the F7 formulation had the highest maximal release of 94.41% in a 24-hr period. The Franz diffusion cell with rat skin in phosphate buffer pH 7.4 was used as the receptor media for *ex vivo* permeation investigations. *Ex vivo* skin penetration testing demonstrated that the medication (74.18%) was released in gradually over the course of 24 hr from the optimized patches. Thus, these patches can be used for systemic delivery of drug via non-parental route. **Conclusion:** The developed transdermal patches may offer sustained and systemic delivery of drugs via non-parental route.

Keywords: Transdermal Patches, Sustained Delivery, Solvent Evaporation Method, Statistical Experimental Designs, Factorial Design, Lisinopril.

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INTRODUCTION

A substitute for oral medication and hypodermic injection is transdermal administration.[1] For centuries, individuals applied medicinal compounds to their skin to achieve medicinal benefits. At present, numerous topical applications have been generated to address specific local indications. Transdermal Drug Delivery Systems (TDDS) are defined as distinct, self-sufficient dosage forms that, when applied to intact skin, allow the drug(s) to be delivered at a controlled pace via the skin and into the systemic circulation.[2] Transdermal route is acknowledged as one possible method for the local and systemic distribution of medications.[3] In 1979, scopolamine was delivered via transdermal patch for three days to cure motion sickness in the United States for systemic delivery.[4] Transdermal Drug Delivery (TDD) is a painless method for systemic delivery of drugs by applying onto intact and healthy skin.[5,6] The medication mostly enters in body through the stratum corneum and subsequently enters in dermis by way of the deeper epidermis, without building up in the dermal layer. The medication penetrated through the dermal layer and through the dermal microcirculation it becomes accessible to systemic absorption.[7,8] The three TDDS generations operate in the following ways: The role of first generation transdermal delivery systems in distribution of small, lipophillic, low-dose medications has been increased steadily. The formulations produced via second-generation delivery systems have been employed chemical enhancers, iontophoresis and non-cavitational ultrasound to adjust distribution rates in pre-requisite time. Third-generation delivery technologies employ microneedles, electroporation, microderm abrasion, thermal ablation, and cavitational ultrasound to target the stratum corneum and skin's barrier layer.[4] Numerous transdermal products with different drugs such as lidocaine, diclofenac, nitroglycerin, clonidine, fentanyl, nicotine, oestradiol, and testosterone were launched in market. Additionally, this interest can be reflected in the large size of the market. Some benefits of transdermal drug delivery systems include avoiding first-pass hepatic metabolism, reducing gastrointestinal side effects, eliminating drug-food interactions, and eliminating the risks and inconveniences associated with

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intravenous therapy.[9] The two main adverse consequences of this method are skin irritation and hypersensitivity responses.[10] Hydrophilic medications have proven challenging to administer transdermally; peptides and macromolecules, such as novel genetic treatments utilizing DNA or small-interfering RNA (siRNA), have presented unique difficulties.[11] A medicinal molecule can traverse the unbroken stratum corneum in three crucial ways.[12] Diffusion can takes place via transcellular and intercellular permeation through the stratum corneum, as well as transappendageal permeation through the sweat, sebaceous, and hair follicles. A given medication is expected to permeate through a combination of these channels, with the physicochemical properties of the molecule determining the proportional contributions of these pathways to the gross flow.[13]

The use of statistical experimental designs in drug formulation facilitates fewer trials and makes it easier to better estimate the relative significant levels of different variables, an important tool for optimizing process variables.[14] The formulation of transdermal patches is optimized by using different designs such as D-optimal design, Box-Behnken Design (BBD) and Factorial design.[15] In the present study, the factorial design with two factors and three levels was used to optimize the process, as it generates few runs than others.[16]

The lysine derivative of enalapril, lisinopril (angiotensin converting enzyme inhibitor), does not require hydrolysis to have pharmacological effect. Its bioavailability ranges from 6 to 60% due to its substantial hepatic first pass metabolism. Transdermal patches have been developed to address the drug's low bioavailability. The medicine has an effective single-daily half-life of 12 hr, but its average intersubject bioavailability is just 25%, which is a serious drawback.[17] Transdermal administration is therefore a potential substitute strategy that will boost the drug's bioavailability and prolong its release. DMSO is utilised in the formulation as a penetration booster to get past the skin's barrier qualities.[18] The present study was proposed to optimize and formulate series of lisinopril-loaded transdermal patches using two factor three level factorial designs for sustained and systemic delivery of drugs via non-parental route by using solvent evaporation method. The intention behind the study was to explore the influence of various independent variables like concentration of ethyl cellulose (A) and concentration of HPMC (B) on the dependent variables like tensile strength and percentage cumulative drug release by using factorial design. We also assessed the material's physical appearance, consistency in thickness and weight, folding endurance, moisture content and uptake percentages, water vapour permeability, tensile strength, *in vitro* drug release studies, and *ex vivo* permeation studies.

MATERIALS AND METHODS

Material

Lisinopril was acquired from Combitic caplet global private limited, located in Sonepat. Loba Chemie Pvt. Ltd., Mumbai, supplied hydroxyl propyl methylcellulose, polyvinyl alcohol, ethanol, and ethyl cellulose. Sodium chloride, disodium hydrogen phosphate, and dibutylphthalate were acquired from Thermo Fischer Scientific, Pvt. Ltd., Mumbai. Qualikens Fine Chemicals Pvt. Ltd., Delhi, was the source of dimethyl sulfoxide. Potassium chloride was acquired from E. Merck Ltd., in Mumbai. Potassium dihydrogen orthophosphate was acquired from RFCL Ltd., New Delhi.

Method

The solvent evaporation technique was employed to produce matrix-type transdermal patches containing lisinopril in varying ratios of ethyl cellulose and hydroxyl propyl methyl celluloses. Pouring a 3% PVA solution into a petridish and drying it at 60°C for 6 hr resulted in the casting of the supporting membrane. The polymeric solution was prepared by dissolving ethyl cellulose and hydroxy propyl methyl cellulose in a solvent (mixture of dichloromethane and ethanol in equal proportion). In order to achieve a homogenous solution, the drug was gradually incorporated into the polymeric solution under magnetic stirring.

As a plasticiser, di-butyl phthalate was employed, and DMSO was employed as a penetration enhancer. Then, the solution was transferred in petridish, and allowed to dry at room temperature. After the patches had dried completely, they were divided into 3×3.6 cm^2 pieces and stored in desiccators until they were needed.[19,20] The drug that was employed in each 3×3.6 cm^2 patch was equivalent to 20 mg. In order to apply the transdermal patch for 24 hr, the dose has been calculated based on the cumulative dose of 10 mg per day. Consequently, the dose is 20 mg. The formulation composition is presented in Table 1 in accordance with the fractional factorial design.

Preliminary Trials of Transdermal Patch

To choose the subject matter domain for the fabrication of the transdermal patch, preliminary testing was conducted. The experimental field shouldn't be too big or small, as this could result in tests that aren't realistic or too far away from the permissible range.

Selection of hydrophobic polymer (A)

Ethyl cellulose was used in numerous studies at varying concentrations. Ethyl cellulose's hydrophobic properties cause its concentration to rise with increased sustained action. The working range of ethyl cellulose was 240 mg to 960 mg. The patches were shown to exhibit poor tensile strength above 960 mg of polymer, and to exhibit declining sustained action below 240 mg of polymer. The hydrophobic nature of ethyl cellulose

declined the percentage of medication release as its concentration rises above 600 mg.

Selection of hydrophilic polymer (B)

To prepare the patch, hydroxypropyl methyl cellulose was tested. It has been demonstrated that incorporating a hydrophilic component during formation an insoluble film will increase its dissolution rate constant because of its hydrophilic character. This is because the aqueous soluble portion of the polymer matrix dissolves and creates gelaneous holes, which in turn shortens the drug molecules' mean diffusion time when they release into the diffusion medium. A rise in drug release percentage is indicated by an initial increase in HPMC concentration. The patch was sticky at doses above 840 mg and difficult to peel at doses below 360 mg. For the purpose of creating the patches, a dosage range of 360 mg to 840 mg was selected.

Design Of Experiment For Preparation Of Transdermal Patch

Using Design Expert Software version 13, a 2-factor, 3-level factorial design can be utilised to explore quadratic response surfaces and build polynomial models. The selection of the two independent variables, namely Ethyl Cellulose (A) and HPMC (B), was based on preparatory studies conducted prior to the implementation of the experimental design.[21] The purpose of the experiment was to determine how several independent factors, such A and B, affected the results. When two factors are adjusted at the same time, the response changes as indicated by the interaction term (AB). The purpose of including the polynomial term (A2, B2) is to explore nonlinearity.

Evaluation of Transdermal Patches

All the prepared formulations were subjected for preliminary screening to verify the effect of various polymer combinations on transdermal patches.[22-24]

FTIR

The FT-IR spectras of Lisinopril, ethyl cellulose, HPMC and optimized batch of transdermal patch were recorded using an Instrument FT-IR-Alpha Bruker 1206 0280 from Germany. The sample holder was first cleaned, and background measurement was then carried out to offset the impact of external contaminants. The samples positioned on holder for analysis and scanned from 400-4000 cm^{-1}at a resolution of 4 cm^{-1}. The spectrum was appeared on the screen after 16 runs.[22,23]

Physical appearance

A visual examination was conducted on each created patch to assess its colour, clarity, flexibility, and smoothness.[24]

Thickness uniformity

The current study's objective was to assess the formed patches' equal thickness. Using a screw gauge, the thickness of the patches was measured three times (n=3), and the average thickness of the three readings was computed.[25]

Weight uniformity

The total weight of three films was determined by weighing each moiety separately.[26]

Folding endurance

It was ascertained by folding a tiny piece of film at the same spot repeatedly until it broke. The value of folding endurance was determined by counting how many times the films could be folded in the same direction without breaking.[24]

Drug content

The small pieces of patches ($1cm^2$) were stirred with teflon coated magnetic bead for 5hr in 100 mL of Phosphate Buffer Saline of pH 7.4 (PBS). The contents were examined for the drug content against the reference solution at 273 nm after filtration using HPLC.[27]

% Moisture content

The produced films were individually weighed and stored for 24 hr at Room Temperature (RT) in desiccators filled with fused $CaCl_2$. Once a day had passed, the films were weighed again, and the percentage moisture content was calculated using formula (n=3):[28]

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final Weight}}{\text{Final Weight}} \times 100$$

% Moisture uptake

In order to maintain an 84% relative humidity, the weighted films were stored in desiccators in presence of a saturated solution of potassium chloride for 24 hr at room temperature. After that change in weight of film were evaluated, and the percentage moisture uptake was calculated using formula (n=3):[28]

$$\% \text{ Moisture Uptake} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100$$

Water vapor permeability

Glass vials were properly sterilized in an oven and filled with fused calcium chloride, and sealed with polymeric films using adhesive tape. After weighing, the vials were stored in humidity chamber at 85% R.H. condition for 24 hr. The vials were weighed at different intervals like 3, 6, 12, 18, and 24 hr to estimate the weight gain (n=3).[29]

Tensile strength

Tensile strength of film was measured by using tensile tester. A strip of film of definite size was cut and was held between jaws of tester and measurement was done by keeping the one jaw stationary and moving other slowly with the help of moving screw until the film broken (n=3).[24]

$$\text{Tensile Strength} = \frac{\text{Tension at break}}{\text{Cross sectional area}}$$

In vitro Drug Release Studies

The paddle over disc assembly was used to evaluate *in vitro* drug release of medicine from patches in Phosphate Buffer of pH 7.4 (900 mL). The patch was positioned in assembly and its surface was covered with muslin cloth. The whole assembly was then positioned in the vessel in such way that the releasing surface of the patch faced upwards. The apparatus was operated at 50 rpm and maintained at 37±0.5°C. The sample were withdrawn regularly after 1hr up to 24 hr and analyzed to estimate the content of drug by HPLC (Agilent technologies 1200 series, Germany; Quaternary pump, Eclipse XDB- C18 column (4.6 mm×150 mm) packed with octadecylsilane and porous silica (3 µm)) at 258 nm.[30,31]

Drug release kinetics

The raw data obtained from *in vitro* release studies were analyzed and fitted into different equations and kinetic models to compute the percent drug release and release kinetics of lisinopril from transdermal patches. These models of data treatment include zero-order kinetic model, first order kinetics, higuchi's model, korsmeyer's-peppas model.

Ex vivo Permeation Studies

Animals: The Institutional Animal Ethics Committee of Hindu College of Pharmacy (585/02/c/CPCSEA) vide reference no. I reviewed and approved the protocol of animal study.[13,32]

Preparation of skin

The entire thickness of the dead rat's skin was removed, and it was then cleaned with water. Fingernails or nails were used to remove the layer of fatty tissue. Hair removal was accomplished with depilatory cream. Wet cotton was used to scrub the hair, and regular saline solution was used to wash it. Until the skin was used for the diffusion investigation, it was stored in a regular saline solution in the refrigerator. The skin was given time to acclimatize to room temperature before usage. Subsequently, skin was adhered between the cell's receptor and donor section. The skin was constricted so that the receptor medium would come into touch with the dermal side.[33]

Diffusion cell

The purpose of the diffusion research was to determine how well drugs penetrated the transdermal system's barrier. *In vitro* studies are also conducted to produce TDDS. Diffusion cells are often employed in two varieties: horizontal and vertical. Diffusion cells of the Franz and Keshary-Chien (K-C) type are horizontal cells. Franz diffusion cell was employed in this study. Typically, diffusion cells consist of two compartments: the donor compartment contains the active content, and the receptor compartment contains the receptor solution. These compartments are divided by a barrier, such as the skin of the rat's abdomen. The temperature-maintaining jacket and sample port made up the cell. Static water existed within the jacket due to the latex tubing connecting the exit and input, and a hot plate was used to provide heat. The receptor solution was stirred using teflon coated bead on magnetic stirrer. The receptor compartment was covered with the rat's abdomen skin, and clamps were used to secure both compartments firmly.[33]

Phosphate buffer pH 7.4 was used as medium in receptor compartment. The buffer was stirred using teflon coated bead at temperature 37±0.5°C. The diffusion was performed for 24 hr and a required amount of sample was withdrawn regularly by replacing with the same volume of phosphate buffer to maintain the sink conditions. The samples were analyzed at 258 nm. Other

Table 1: Composition of different formulations according to fractional factorial design.

Formulation	Drug (mg)	Factor A Ethyl Cellulose (mg)	Factor B HPMC (mg)	DBP (30%) (mL)	DMSO (mL)
F1	120	240	360	0.35	1
F2	120	600	360	0.35	1
F3	120	960	360	0.35	1
F4	120	240	600	0.35	1
F5	120	600	600	0.35	1
F6	120	960	600	0.35	1
F7	120	240	840	0.35	1
F8	120	600	840	0.35	1
F9	120	960	840	0.35	1

designs of diffusion cells that are in existence include Valia-Chien (V-C) cell, Ghannam-Chien (G-C) cell, Jhawer-Lord (J-L) Rotating disc system, etc.

RESULTS

Lisinopril was stored with different additives and polymers at 25°C/60% RH and 40°C/75% RH for 4 weeks to check their compatibility and observed the physical changes like colour change, gas or odor formation and liquification (n=3) (Table 2).

Preparation of transdermal patches

The major purpose of the present study was to create a transdermal patch that contained lisinopril by employing Design of Experiments (DOE). A second-order polynomial equation was derived using a two-factor, three-level (3^2) factorial design in order to create contour plots for response prediction. Nine runs in all were produced, with the hydrophobic polymer concentration (A) and the hydrophilic polymer concentration (B) at low, medium, and high levels chosen as independent variables. The percentage of medication release and tensile strength were the dependent variables under investigation. To determine the composition of the optimal formulation, contour plots and response surface plots were created, and a polynomial equation was produced. Generally speaking, the rate of drug release reduced as polymer (A) concentration increased, whereas thickness increased as plasticizer and polymer concentration increased. The design additionally demonstrated the function of contour plots and generated polynomial equations in forecasting the values of dependent variables for the production and enhancement of film formulation.

Preliminary trials

The preliminary trials were conducted to select independent variables and their experimental domain. According to published research, hydrophobic and hydrophilic polymers are the two primary independent variables of a patch. An evaluation was done on a number of studies using varying concentrations of EC. The increased concentration of EC from 240 mg to 960 mg depicted a significant decrease in % drug release but increased in thickness. Initial increase in the concentration of HPMC shows increase in % drug release and tensile strength. The patch with concentration less than 360 mg was not easily detachable and at concentration of 840 mg it was sticky in nature. Hence the percentages between 30-70% of HPMC were trialed. After selection of independent variables and their working range, 3^2 factorial designs were applied to generate formulation trials with various combinations of levels of factors (independent variables).

Formulation using RSM

Experimental design is a powerful and efficient tool for the development of a formulation. The experimental design allows for studying different processing parameters that influenced the selected responses with minimum number of experiment. Thus, reducing the time and cost required for the development of formulation. Response Surface Methodology (RSM) is a widely employed approach for the development and optimization

Table 2: Affinity study of drug with additives/polymers.

Drug-Excipients (1:1)	At 25°C/ 60% RH				At 40°C/ 75% RH			
	1st Week	2nd Week	3rd Week	4th Week	1st Week	2nd Week	3rd Week	4th Week
Drug + Ethyl Cellulose	√	√	√	√	√	√	√	√
Drug + HPMC	√	√	√	√	√	√	√	√
Drug + HPMC + EC	√	√	√	√	√	√	√	√
Drug + PVA	√	√	√	√	√	√	√	√

*√ refers to no changeNo physical incompatibilities were observed with any of the excipients.

Table 3: Levels of independent variables used in fractional factorial design and result of tensile strength and cumulative drug release from lisiniopril transdermal patches.

Batch No.	A: EC (mg)	B: HPMC (mg)	Thickness (mm)	Tensile strength (kg/mm²)	*In vitro* drug release (%)
F1	+1(960)	-1(30)	0.35±0.08	3.38± 0.14	85.59±7.5
F2	0(600)	1 (70)	0.39±0.12	3.31±0.08	75.14±6.9
F3	+1(960)	-1(30)	0.46±0.05	3.41±0.65	68.64±7.3
F4	-1(240)	0 (50)	0.34±0.06	3.36±0.35	89.34±6.5
F5	0 (600)	0 (50)	0.38±0.09	3.33±0.19	83.54±6.2
F6	+1(960)	0 (50)	0.44±0.04	3.43±0.32	80.97±5.7
F7	-1(240)	+1 (70)	0.31±0.09	3.54±0.40	94.41±8.7
F8	0 (600)	+1 (70)	0.33±0.06	3.46±0.58	90.52±7.4
F9	+1(960)	+1 (70)	0.41±0.059	3.49±0.63	93.24±8.6

of drug delivery carriers. The Design of Experiment (DOE), methodology involving various types of experimental design, generation of polynomial equations and mapping of the responses over the experimental domain is used to determine the optimum formulations.[34]

The polynomial equation generated by the experimental design is given as:

$$Y=b0 + b1A+ b2B + b12AB + b11A2+ b12B2$$

Where Y is the response evaluated, b_o is the arithmetic mean response of 9 runs, b_i is the estimated coefficient of independent variables.

The main effects (A and B) represent the average result of changing 1 factor at a time from its low to high value. The interaction term (AB) show how the response changes when 2 factor are simultaneously changed. The polynomial terms (A^2 and B^2) were included to investigate non- linearity.[35]

Tensile Strength, thickness and *in vitro* drug release

Tensile Strength, thickness and *in vitro* drug release ranged from 3.38±0.14 to 3.54±0.40 kg/mm², 0.31±0.08 to 0.46±0.05 mm, 85.95±0.38 to 93.24±0.49%, respectively (Table 3). Formulation F7 has maximum tensile strength, minimum thickness and maximum *in vitro* release (0.31±0.08, 3.54±0.40 kg /mm², 94.41±0.49%, respectively). Figures 1 and 2 display the pareto chart, 3D-response surface plots, and corresponding contour plots illustrating the tensile strength and *in vitro* release of transdermal patches. Quadratic equations were developed to represent the relationship between the dependent and independent variables.

Tensile Strength= +3.33+0.008A+0.065B-0.020AB+0.068A2+0.058B2

Where A, B are the main effects; AB is the interaction term and A^2 and B^2 are square terms. The tensile strength's F-value (10.68) and *p*-value (0.0397) indicated that the model is significant.

In vitro Drug Release

The release of drug range between 68.64±7.3to 94.41±8.7%. A Pareto chart was prepared to analyse the effect of coefficient on *in vitro* drug release (Figure 1 (II)). The 3D response surface plots are depicted in Figure 2. The polynomial equation was generated using Design Expert software. The F-value (289.65) and *p*-value (0.0003) for *in vitro* release indicated that the model is significant.

In vitro Drug Release = +83.08-4.42A+8.13B+3.94AB+2.30A2-0.027B2

The *p*-value less than 0.0500 indicate that the model terms are significant. Values greater than 0.10 indicate the model terms are not significant (Table 4). The ANOVA data of the quadratic model for tensile strength implies that the model is significant with F-value of 10.68. In this case B, A^2 are significant model terms. There is only a 3.97% chance that this lack of fit value could occur due to noise. The R^2, predicted R^2 and adjusted R^2 values for ANOVA data of tensile strength were 0.9468, 0.3527 and 0.8582% respectively. Signal to noise ratio (Adeq Precision) greater than 4 is desirable. A ratio of 9.010 indicates an adequate signal. This

Table 4: ANOVA results for quadratic model of tensile Strength and Cumulative drug Release.

Source	Sum of Squares	d_f	Mean Square	F- Value	*p*-value	Remark
Tensile Strength						
Model	0.044	5	0.0087	10.68	0.0397	Significant
A-EC	0.000417	1	0.000417	0.51	0.5262	
B-HPMC	0.025	1	0.025	31.11	0.0114	
AB	0.0016	1	0.0016	1.96	0.2557	
A^2	0.0093	1	0.0093	11.46	0.0429	
B^2	0.0068	1	0.0068	8.35	0.0630	
Residual	0.0024	3	0.00081			
Cor Total	0.046	8				
Cummulative % Drug Release						
Model	586.68	5	117.34	289.65	0.0003	Significant
A-EC	116.95	1	116.95	288.71	0.0004	
B-HPMC	396.91	1	396.91	979.79	< 0.0001	
AB	62.25	1	62.25	153.67	0.0011	
A^2	10.56	1	10.56	26.08	0.0145	
B^2	0.0014	1	0.0014	0.0035	0.9565	
Residual	1.22	3	0.41			
Cor Total	587.89	8				

model can be used to navigate the design space. In case of *in vitro* release, the model F-value of 289.65 implies the model is significant. There is only a 0.03% chance that the F-value could be large due to noise. The R^2, Predicted R^2 and adjusted R^2 values for ANOVA data of *in vitro* release were 0.9979, 0.9786 and 0.9945% respectively. The value of adequate precision (48.293) indicates an adequate signal.

FT-IR

FT-IR was used to study the chemical interaction between drugs and the polymeric material. The infrared spectra of formulation evidenced that the functional groups responsible for antihypertensive and analgesic action of the drug were unaffected.[36] The main peak in the spectrum of the drug lisinopril, both free and with polymers is almost same. The characteristic peaks were observed at wave numbers 1652, 1575, 1456, 1342, 748, 700 cm^{-1}. The presence of peaks between 3886.37-3567.01 cm^{-1} depicted N-H stretch, peak at 1652.82cm^{-1} evidenced presence of C=O functional group (1870-1650cm^{-1}). Peak at 1506.67cm^{-1} confirmed the presence of C-O-C. Concurrently, peak at 700.73 cm^{-1} demonstrated the presence of C-C stretching. IR spectras of lisinopril, EC, HPMC and optimized formulation are shown in Figure 3a and Figure 3b.

Evaluation of Transdermal Patches

Physical appearance

The prepared transdermal patches were depicted smooth, transparent, and flexible (Figure 4). The outcome evidenced that the methods adopted to prepare these patches was satisfactory. The results of thickness uniformity, weight uniformity, folding endurance, drug content, % moisture content, % moisture uptake, water vapor transmission and tensile strength (n=3) were depicted in Table 5.

In vitro drug release study

To anticipate consistency of the rate and duration of drug release, release studies are necessary. It is widely recognized that polymer dissolution plays a crucial role in drug release from matrices, guaranteeing the effectiveness of sustained release. In our *in vitro* release investigations, we used the paddle over disc technique. The results demonstrated that the drug release rapidly from the patch as the concentration of HPMC augmented due to its hydrophilic nature.[36,37]

The formulation F7 depicted maximum release i.e. 94.41% in 24 hr. Batch F3 showed minimum release due to higher concentration of hydrophobic ethyl cellulose (Table 6). The release kinetics was evaluated by making use of zero order, first order, Higuchi

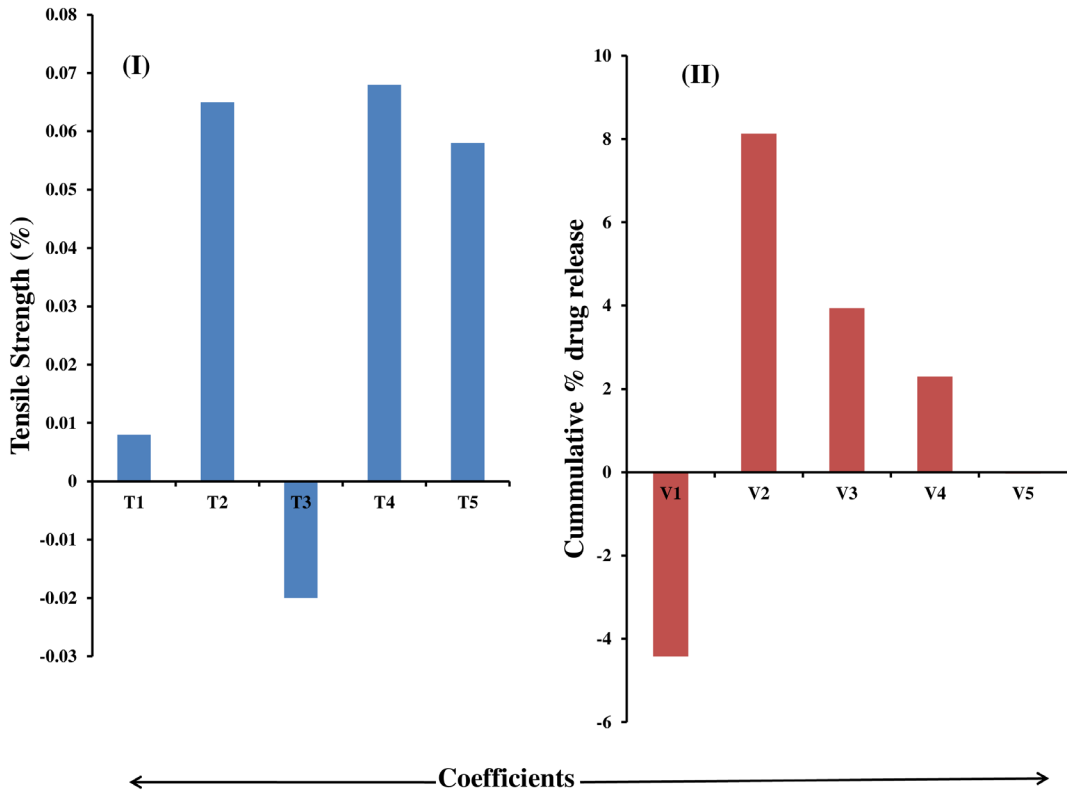

Figure 1: Upshot plot of coefficients on (I) percentage Tensile Strength (T1, and T2, are coefficients of main effects (A and B); T3 is coefficients of interaction term (AB); and T4 and T5 are coefficients of square terms (A2 and B2); (II) Cumulative % Drug Release (V1, and V2 are coefficients of main effects (A and B); V3 is coefficients of interaction term (AB); and V4 and V5 are coefficients of square terms (A2 and B2).

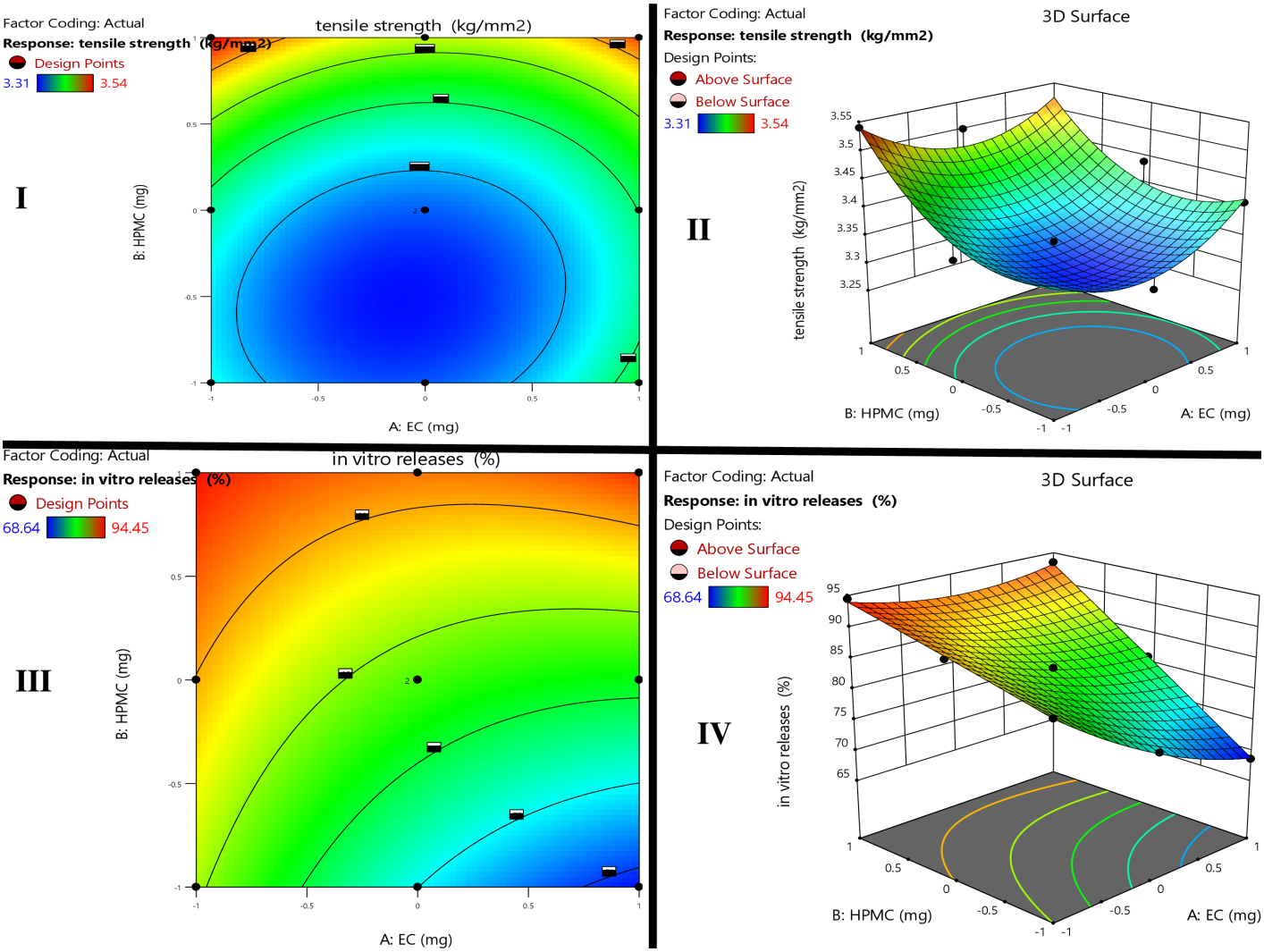

Figure 2: Response surface plots and contour plots showing the influence of level of ethyl cellulose and HPMC on tensile strength and cumulative % drug release from transdermal patches.

Table 5: Characteristic parameters of Transdermal patches.

Batch	Thickness (mm)±SD	Weight variation (mg)±SD	Folding endurance±SD	% Drug content	% Moisture content	% Moisture uptake	Water vapour transmission (g/cm².24h)
F1	0.35±0.08	374±0.31	329±4.32	96.59±0.57	3.7±0.56	3.42±0.27	0.357±0.052
F2	0.39±0.12	429±0.37	315±3.0	93.84±0.52	2.8±0.68	3.1±0.36	0.276±0.030
F3	0.46±0.05	490±0.44	286±5.21	98.35±0.50	2.5±0.39	2.89±0.79	0.251±0.038
F4	0.34±0.06	365±0.30	340±3.87	97.62±0.51	3.9±0.33	3.62±0.74	0.386±0.049
F5	0.38±0.09	392±0.38	320±4.60	96.54±0.55	3.4±0.31	3.35±0.37	0.322±0.051
F6	0.44±0.04	472±0.45	292±4.15	94.97±0.53	3.1±0.52	3.26±0.59	0.301±0.035
F7	0.31±0.09	320±0.35	356±3.89	99.62±0.56	5.4±0.42	4.51±0.38	0.439±0.023
F8	0.33±0.06	360±0.39	341±5.10	96.82±0.55	4.1±0.53	3.86±0.54	0.406±0.029
F9	0.41±0.07	456±0.42	304±5.15	98.74±0.60	4.9±0.38	4.19±0.72	0.427±0.059

equation and Korsmeyer's equation (Table 7). It was observed that Korsmeyer's peppas release kinetic was best suited based on R^2 value.

Diffusion studies

The figure displays the cumulative percentage of medication that permeated through rat skin over time, as represented graphically, from the best batch (Figure 5). An overall range of 59.97–74.18% was observed for the percentage of drug penetration from various formulation batches. According to the results, Higher Percentages of Hydrophilic Polymers (HPMC) clearly increase the penetration rate (Table 8).

Batch F3 has higher concentration of ethyl cellulose that slows down skin permeation that leads to decrease in permeability up to 59.97%.The first order, zero order, Higuchi, and Korsmeyer's equations were among the equations to which the *ex vivo* permeation data was fitted. We computed and compared the coefficient of correlation for every kinetic. Since none of the transdermal patch formulations' *ex vivo* permeation profiles fit perfectly to zero order behavior, Korsmeyer's equation which demonstrates that permeation follows diffusion mechanism best captures these data. According to *ex vivo* skin penetration testing, batch F7 released most of the medication (74.18%) in a sustained release pattern over the course of 24 hr that makes it a better formulation.[38]

Table 6: % Cumulative Drug Release of Lisinopril from different batches.

Time (Hr)	% Cumulative Drug Release of Lisinopril								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	8.32±0.8	6.93±0.5	7.26±0.7	8.53±0.4	9.61±0.5	8.01±0.6	7.42±0.5	8.72±0.7	8.79±0.7
2	13.87± 1.4	11.80±0.9	10.18±1.1	12.82±0.9	15.26±1.1	12.73±1.2	12.82±1.5	14.82±1.4	16.58±1.1
3	16.42±1.5	16.27±1.2	14.35±1.2	15.69±1.3	21.34±1.3	17.64±1.5	15.69±1.9	20.63±1.8	20.62±1.4
4	21.53±1.8	23.50±1.5	19.96±1.7	18.37±1.4	25.80±1.2	22.12±1.9	19.28±1.8	24.34±2.1	24.27±1.6
5	25.76±1.9	27.65±1.6	24.56±2.2	23.26±1.5	34.12±1.8	27.14±1.2	23.62±2.1	29.56±2.2	29.87±1.9
6	35.82±2.5	33.25±2.5	34.64±2.5	32.76±2.2	42.65±2.3	39.58±2.1	33.08±2.3	38.71±2.3	38.04±2.4
7	41.52±3.2	37.69±2.6	39.57±2.6	35.64±2.4	46.89±2.7	45.26±2.5	36.64±2.5	43.68±2.4	43.48±2.8
8	41.52±3.5	37.69±1.7	39.57±2.7	35.64±2.6	46.89± 2.9	45.26±2.6	36.64±2.1	43.68±2.6	43.48±2.9
9	47.96±3.7	41.32±1.9	44.96±2.9	38.94±3.1	51.37±3.2	51.59±2.9	41.94±3.1	49.87±2.7	46.56±2.7
10	52.81±4.2	46.54±2.1	48.21±3.5	44.69±3.1	56.48±3.1	54.82±2.7	47.73±3.2	53.36±2.9	49.30±3.1
11	56.24±4.1	51.97±2.3	54.48±4.2	48.83±3.5	63.11±3.3	56.41±3.1	56.86±3.9	59.61±3.1	54.85±3.3
12	63.86±4.8	59.42±1.9	58.73±4.1	57.39±3.2	71.79±3.7	62.36±3.6	70.94±3.5	72.24±3.2	69.49±3.5
24	85.59±7.5	75.14±6.9	68.64±7.3	89.34±6.5	83.54±6.2	80.97±5.7	94.41±8.7	90.52±7.4	93.24±8.6

Table 7: Kinetics of drug release of optimized formulation in phosphate buffer solution pH 7.4.

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
F7	R^2	K_o	R^2	K_f	R^2	K_h	R^2	N
	0.794	3.5876	0.592	-0.065	0.923	9.1784	0.948	1.0084

Table 8: *Ex vivo* permeation study of F1 to F9 across rat skin.

Time (Hr)	% Drug permeated in 24 hr								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	6.04	3.94	3.35	4.11	4.50	4.85	4.68	5.51	5.68
2	9.83	5.21	6.21	8.39	7.25	6.25	7.52	12.79	8.71
3	13.24	10.59	10.59	15.75	10.48	10.72	13.60	17.71	15.91
4	17.57	15.82	15.82	20.92	16.20	15.79	21.95	23.33	24.56
5	23.04	21.56	21.56	26.23	22.75	21.30	29.87	27.52	29.87
6	29.68	25.21	24.51	31.57	26.49	26.93	33.56	35.75	36.54
7	36.84	31.40	28.40	37.75	31.96	32.52	39.10	41.24	42.12
8	41.52	36.54	34.94	42.50	36.78	38.89	45.21	46.68	47.03
24	70.78	57.92	56.67	71.34	57.98	59.46	74.18	65.75	71.19

DISCUSSION

The solvent evaporation technique was employed to produce matrix-type transdermal patches containing lisinopril in varying ratios of ethyl cellulose and hydroxyl propyl methyl celluloses.A 2-factor, 3-level factorial design was used to prepare transdermal patches using Design ExpertSoftware version 13. All the prepared formulations were subjected for preliminary screening to verify the effect of various polymer combinations on transdermal patches. No physical change was depicted in the vials containing both drugs and polymers/excipients after 2 to 4 weeks, which evidenced the compatibility of drug with selected excipients. The preliminary trials were conducted to select independent variables and their experimental domain. According to published research, hydrophobic and hydrophilic polymers are the two primary independent variables of a patch. An evaluation was done on a number of studies using varying concentrations of EC to select the independent variables and their working range. After selection of independent variables and their working range, 3^2 factorial designs were applied to generate formulation trials with various combinations of levels of factors (independent variables). Quadratic equations were developed to represent the relationship between the dependent and independent variables.

FT-IR was used to study the chemical interaction between drugs and the polymeric material. All peaks were observed in the finger print region of FT-IR spectra. This evidenced that there is no drug - excipients interaction. All the characteristic peaks of drug and polymers were found to be intact in FT-IR spectra of optimized formulation which indicates that there is no chemical interaction between drug and polymer. The thickness of patch was measured at different locations of patch with the help of screw gauze and average of thickness was calculated. The result demonstrated thickness variation of patch was ranged from 0.310 mm to 0.460 mm with low standard deviation. The patches exhibited uniform weight between 320 mg to 490 mg with low standard deviation values. The folding endurance test is used to estimate the brittleness of patch. It was observed that folding endurance of patches decreases with augmentation of ethyl cellulose. The

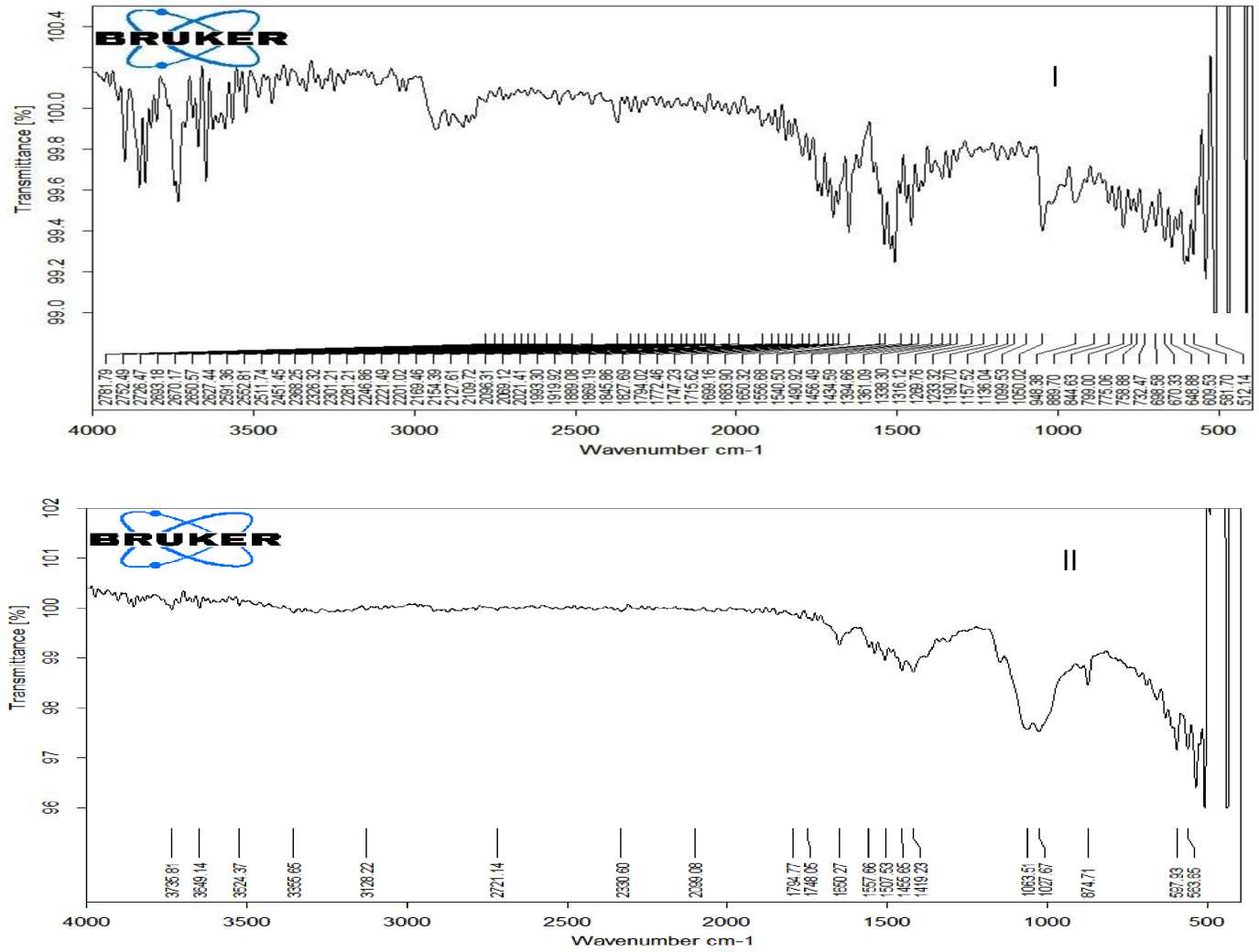

Figure 3a: IR spectrum of (I) Lisinopril (II) Ethyl cellulose.

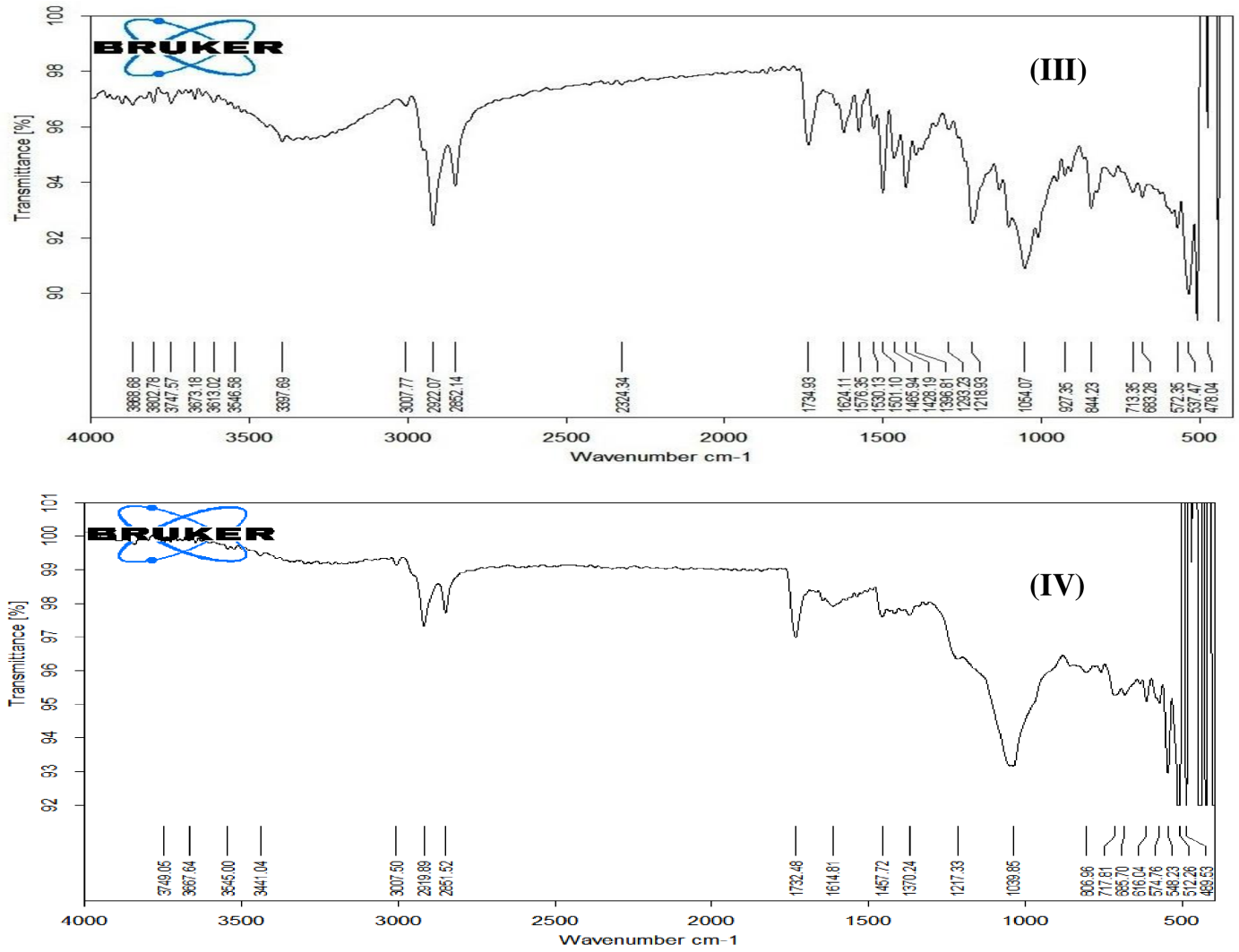

Figure 3b: IR spectrum of (III) HPMC (IV) Optimized formulation.

results demonstrated that the method employed to prepare films are capable to produce films with uniform drug distribution. % drug content of patches was found in range between 93.84 to 99.62% which is satisfactory. The moisture content of the formulations was increased with rise in concentration of HPMC and decreased as quantity of EC was increased. The small amount of moisture increased their stability and converted them into dried and brittle films. The moisture uptake of patches was found to augment with the increase in amount of HPMC and decrease with the increase in concentration of EC. Determination of Water Vapor Transmission (WVT) helped in estimation of the permeability potential of patches. The results demonstrated that all formulations were permeable to water vapour. The formulations with highest EC concentration depicted least WVT due to its hydrophobic nature and formulations with highest conc. of HPMC showed maximum WVT due to its hydrophilic nature. The capacity to sustain rupture is measured by tensile strength. Due to the polymer's hydrophobic properties, patches with higher EC concentrations had higher tensile strengths, but patches with higher HPMC concentrations had lower tensile strengths. The results demonstrated that the drug release rapidly from the patch as the concentration of HPMC augmented due to its hydrophilic nature. The formulation F7 depicted maximum release i.e. 94.41% in 24 hr. Batch F3 showed minimum release due to higher concentration of hydrophobic ethyl cellulose. The release kinetics was evaluated by making use of zero order, first order, Higuchi equation and Korsmeyer's equation. It was observed that Korsmeyer's peppas release kinetic was best suited based on R^2value. *Ex vivo* investigations utilizing rat skin as a membrane barrier allowed researchers to examine how much quantity of polymers affects medication permeability. The leaching process of HPMC, porosity, as well as the polar nature of this polymer, might be the reason of the increase release rate of drug from HPMC patches. As a result, the area of the exterior film exposed to the solvent increases that increases the interior porosity and decreases the tortuosity. According to *ex vivo* skin penetration testing, F7 released most of the medication (74.18%) in a sustained release pattern over the course of 24 hr that makes it a better formulation.

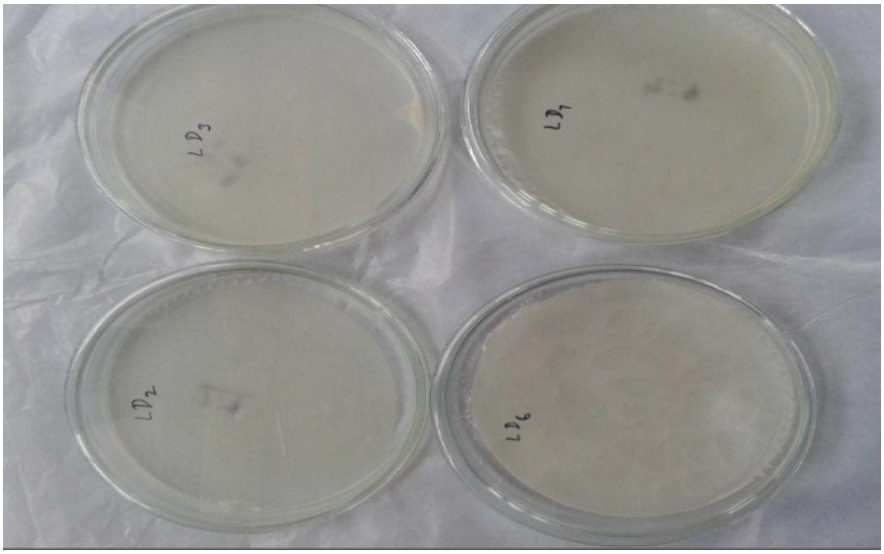

Figure 4: Prepared transdermal patches.

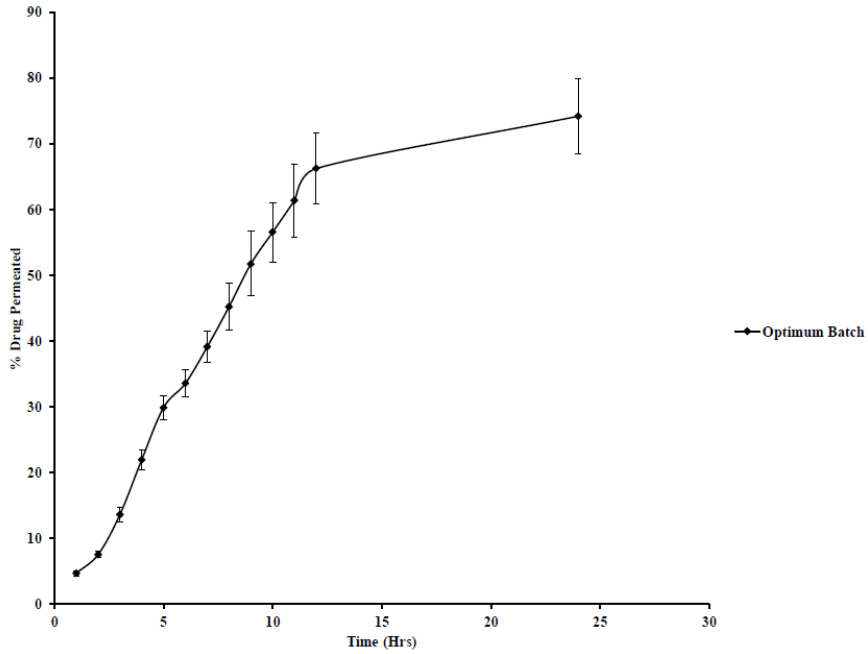

Figure 5: Graphical representation of *ex vivo* permeation study of F7 across rat skin.

CONCLUSION

Lisinopril is an antihypertensive medication that is used to prevent diabetic nephropathy, acute myocardial infarction, and hypertension. It's an inhibitor of the Angiotensin Converting Enzyme (ACE). Its half-life is brief and its first pass metabolism is not constant. Because it must be given two or three times a day, patients don't comply well. The goal of this work was to develop and assess TDDS of lisinopril for sustained release using the solvent evaporation method. This medication was a promising option for the development of a transdermal patch due to its small molecular size, excellent permeation, and short half-life. The primary goals in developing the transdermal system were to increase adherence among patients, decrease the frequency of dosing, and prolonged duration of drug release. The exterior appearance, weight homogeneity, bending strength, humidity level, humidity uptake, water vapour permeability, *in vitro* drug release investigations, and *ex vivo* permeation experiments were all assessed for the produced patches. The capacity of the patches to tolerate folding was tested using a folding endurance test. The results evidenced the satisfactory folding endurance of all patches. The drug content was found to be uniform in all the formulations ranging from 93.84% to 99.62% which indicated uniform drug distribution. % moisture content and moisture uptake was found to be quite satisfactory which help them to remain stable and dry. Patches containing more EC have less tensile strength and patches containing more HPMC have more tensile strength. *In vitro* drug release study was carried out for all the formulations and it was observed that F7 formulation has maximum release of 94.41% in 24 hr. *Ex vivo* permeation studies were carried out using Franz

diffusion cell on rat skin in phosphate buffer pH 7.4 as a receptor medium. The formulation F7 showed maximum permeation of 74.18% in 24 hr and followed the Korsmeyer's- peppas model for drug diffusion. The outcomes from the present studies evidenced the possibility of sustained and systemic delivery of drugs via non-parental route and scope of further study for the development of lisinopril transdermal patches.

ABBREVIATIONS

TDDS: Transdermal drug delivery systems; **siRNA:** Small-interfering RNA; **BBDBox:** Behnken Design; **HPMC:** Hydroxyl propyl methylcellulose; **DMSO:** Dimethyl sulfoxide; **HPLC:** High Performance Liquid Chromatography; **DOE:** Design of experiments; **EC:** Ethyl Cellulose; **RSM:** Response surface methodology; **WVT:** Water vapor transmission.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

In this research work, solvent evaporation technique was employed to produce Lisinopril loaded transdermal patches with varying ratios of ethyl cellulose and hydroxyl propyl methyl celluloses. Using Design Expert Software version 13, a 2-factor, 3-level design was utilised to explore quadratic response surfaces and build polynomial models. The exterior appearance, weight homogeneity, bending strength, humidity level, humidity uptake, water vapour permeability, *in vitro* drug release investigations, and *ex vivo* permeation experiments were all assessed for the produced patches. The results evidenced the satisfactory folding endurance of all patches. The drug content was found to be uniform in all the formulations which indicated uniform drug distribution. % moisture content and moisture uptake was found to be quite satisfactory which help them to remain stable and dry. The outcomes from *in vitro*drug release of F7 formulation have shown maximum release. *Ex vivo* permeation studies have depicted maximum permeation and followed the Korsmeyer's-peppas model for drug diffusion. The outcomes from the present studies evidenced the possibility of painless sustained and systemic delivery of drugs.

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