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FORMULATION, OPTIMIZATION AND EVALUATION OF TRANSDERMAL PATCHES CONTAINING BENIDIPINE

Neha Katiyar [*1], Pankaj Mishra [2] and Pushpendra Kannojia [2]

BIU College of Pharmacy [1], Rohilkhand College of Pharmacy [2], Bareilly International University, Bareilly - 243006, Uttar Pradesh, India.

Keywords:

Transdermal drug delivery systems, Transdermal Patches, Benidipine, Calcium channel blocker

Correspondence to Author:
Neha Katiyar

Ph.D Research Scholar,
BIU College of Pharmacy,
Bareilly International University,
Bareilly - 243006, Uttar Pradesh,
India.

E-mail: katiyarneha40@gmail.com

ABSTRACT: The study focused on the formulation, optimization, and evaluation of benidipine transdermal patches to overcome the drug's low oral bioavailability and short half-life. FTIR analysis confirmed compatibility between benidipine and selected excipients (HPMC K-100, CMC, PEG-400, Tween-20), showing no significant peak shifts. Patches (F1–F12) were prepared by solvent casting with varying polymer concentrations and evaluated for physicochemical properties, all of which were within acceptable limits, indicating good uniformity and mechanical strength. *In-vitro* release studies showed an initial burst followed by sustained release for 48 hours, with F5 and F7 exhibiting superior drug release. Central Composite Design identified HPMC K-100 and CMC levels as key factors influencing drug release, moisture content, and permeation, with higher polymer concentrations decreasing release due to increased matrix density. Optimization selected F4 as the best formulation, offering controlled release, high drug content, and improved permeation, suggesting strong potential for sustained antihypertensive therapy.

INTRODUCTION: Transdermal drug delivery systems (TDDS) have emerged as an attractive alternative to conventional oral and parenteral routes due to their ability to provide controlled and sustained drug release, improve bioavailability, enhance patient compliance, and minimize first-pass hepatic metabolism [1, 2]. By delivering drugs directly through the skin into systemic circulation, transdermal patches overcome limitations such as gastrointestinal degradation, poor absorption, and frequent dosing requirements [3].

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Advances in polymer technology and permeation enhancement strategies have significantly expanded the scope of TDDS for various therapeutic agents, particularly for drugs used in chronic conditions where long-term, steady plasma concentrations are desirable [4].

Benidipine, a dihydropyridine calcium channel blocker, is widely prescribed for hypertension and angina pectoris [5]. Despite its therapeutic efficacy, Benidipine suffers from limitations such as short biological half-life, low oral bioavailability due to extensive first-pass metabolism, and the need for frequent dosing [6]. These pharmacokinetic drawbacks make it an ideal candidate for transdermal delivery, which can maintain steady-state drug levels, reduce dosing frequency, and improve therapeutic outcomes [7]. In addition, the rationale for selecting a 48-hour transdermal patch

has been clarified. The revised text explains that the prolonged patch duration was chosen to maintain therapeutically relevant plasma concentrations over an extended period, minimize peak–trough fluctuations, and improve patient adherence compared with once- or twice-daily oral dosing. However, formulating an effective transdermal system requires careful optimization of polymers, plasticizers, and permeation enhancers to achieve desirable physicochemical properties, mechanical strength, and controlled drug release [8]. Therefore, the present study aims to formulate, optimize, and evaluate transdermal patches containing Benidipine using suitable polymers and excipients to achieve sustained drug release and improved therapeutic performance. Various formulations were prepared, characterized for physicochemical parameters, and subjected to *in-vitro* drug release studies to identify the optimized patch capable of providing effective transdermal delivery of Benidipine.

MATERIALS AND METHODS:

Materials: Benidipine was received as a gift sample from Nikasn Pharmaceutical, Gujarat, India. HPMC K-100, Polyethylene Glycol 400 (PEG 400) and Tween 20 were procured from Modern Industries. Methanol and ethanol were purchased from Fine Chem Laboratories.

Drug Excipients Compatibility Studies: To check for any changes in the drug's chemical composition following its combination with the excipients/polymers. Powder mixed with potassium bromide was applied and pressed into the shape of a disc. The disc was examined using Shimadzu FTIR spectroscopy (4000-400cm^{-1}) [9].

Preparation of Standard Calibration Curve of Benidipine: Benidipine standard stock solution was prepared by dissolving 10mg of the drug with 10ml of methanol to give a 1000µg/ml concentration. To develop stock II, which has a concentration of 100µg/ml, take 1ml of this stock solution and diluted it with methanol (solvent) up to 10ml. A 10ml volumetric flask was filled with 1ml of the stock solution (100µg/ml) and the line was then filled with methanol to a volume equal to 10µg/ml. The sample was then scanned with a UV-Visible spectrophotometer in the 200-400nm wavelength range using methanol as a blank. Further dilutions of 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml, 12µg/ml, and 14µg/ml were made from the stock solution (100µg/ml). The absorbance of the dilutions was measured at absorption maxima. The calibration curve was then constructed.

Characterization Parameters of Transdermal Patches: The evaluation of patches involved several quality assessment parameters. Thickness was measured at three distinct points on each patch using a micrometer, and mean values were recorded. Uniformity of weight of transdermal patches was determined by selecting three to five patches at random. The protective liner, if present, was carefully removed and each patch was weighed individually using an analytical balance. The average weight of the patches was calculated and the percentage deviation of individual patch weights from the average weight was determined to evaluate uniformity [10].

Drug content of transdermal patches was evaluated by randomly selecting three patches and cutting them into small pieces. The pieces were transferred into a volumetric flask containing a suitable solvent such as methanol or phosphate buffer (pH 7.4). The mixture was sonicated or shaken continuously for 24 hours to ensure complete extraction of the drug from the polymeric matrix. The resulting solution was filtered to remove insoluble matter and suitably diluted with the same solvent. The absorbance of the solution was measured using a UV–Visible spectrophotometer at the specified wavelength [11].

Flatness was evaluated by cutting one strip from the center and two from the sides of each patch, measuring their lengths, and calculating percent constriction, where 0% constriction corresponds to 100% flatness [12]. Folding endurance was determined by repeatedly folding a film at the same spot until it broke, with the final value representing the number of folds the film could withstand without cracking or breaking [13]. Tensile strength of transdermal patches was determined using a tensile strength testing apparatus. The transdermal patch was cut into strips of uniform dimensions and fixed between two clamps of the instrument. One clamp was kept stationary while the other was made movable.

The load was gradually increased until the patch broke. The force required to break the patch and the dimensions of the patch were noted. Tensile strength was calculated to evaluate the mechanical strength and integrity of the transdermal patch. The tensile strength was calculated using the formula:

Tensile strength = Cross-sectional area of the patch /Breaking force [14]

Percentage moisture content was determined by weighing the patches initially, keeping them in a desicator maintained at 75-84% relative humidity (RH) with desiccant (Silica gel) at room temperature for 24 h. The films were weighed again after a specified interval until a constant weight was achieved. The moisture content was calculated using the formula:

% Moisture content = (Initial weight – Final weight) / Final weight × 100 [15]

For percentage moisture uptake, the patches were first kept in a desiccator for 24 hours at room temperature, then transferred to a desiccator maintained at 84% relative humidity using a saturated potassium chloride solution until a constant weight was reached. Moisture uptake was calculated using the formula:

% Moisture uptake = (Final mass – Initial mass) / Initial mass × 100

***In-vitro* Drug Release Studies:** The release rate of benidipine containing transdermal patches was determined by diffusion process using cellophane/dialysis membrane. The diffusion process was performed using (20-50ml) of dissolution media as buffer solution of phosphate (pH 7.4) at 37 ± 0.5° and 100 rpm. The sample (2ml) of the solution was taken from the apparatus at different time periods. The samples were replaced with fresh dissolution media. The samples were diluted if necessary. Absorbance values of these solutions were recorded at maximum Wavelength of Benidipine using UV Spectrophotometer. The percentage drug release was calculated [17].

***Ex-vivo* Skin Penetration Studies:** A Franz diffusion cell with a receptor compartment capacity of 22.5-40 mililitres was used for *ex-vivo* skin penetration study. The animal skin was attached to the diffusion cell's donor and receptor compartments. The formulation patch was applied to the skin and covered with paraffin film. The diffusion cell's receptor compartment was filled with buffer solution pH 7.4. The entire assembly was mounted on a magnetic stirrer, and the solution in the receptor compartment was continually swirled at 50 rpm using magnetic beads, with the temperature maintained at 32±0.5 °C. The samples were taken at various intervals and spectrophotometrically evaluated for drug concentration. At each sample withdrawal (2ml), the receptor phase was replaced with an equal volume of buffer solution. Time was displayed against the cumulative percentages of drug penetrate per square centimetre of patches.

RESULTS AND DISCUSSION:

Benidipine-excipients Compatibility: The benidipine-excipients compatibility study was also conducted in which FTIR spectrum analysed in single and in combination as well. In infrared spectral analysis, benidipine with other excipients have not shown any significant fluctuation. Therefore, it indicates that benidipine is compatible with the excipients *i.e.*, Polyethylene Glycol 400, HPMC K-100 and Tween 20 used in the preparation of the transdermal patches of benidipine.

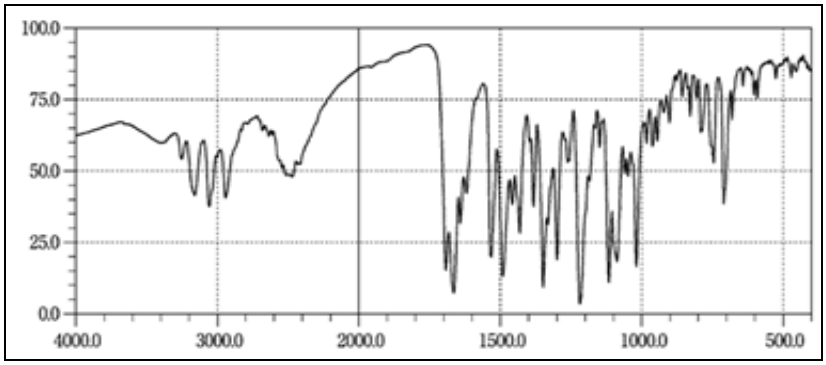

FIG. 1: FTIR SPECTRUM OF BENIDIPINE (SAMPLE)

TABLE 1: IR SPECTRUM INTERPRETATION OF BENIDIPINE SAMPLE

S. no.	Functional groups	Absorption of Benidipine at Wave number (cm^{-1})
1	Aromatic C-H group	3170
2	Aromatic C-H group	3065
3	$-CH_3$, $-CH_2$ groups	2946
4	Ester C=O group	1709
5	C=O group	1668
6	NO_2 group	1532
7	C=C	1492
8	CH bending in CH_3-N group	1429
9	NO_2 group	1347
10	C-N group	1301
11	C-O-C group	1209
12	C-O-C group	1096
13	C-N-H group	1011
14	C-N bending in aromatic ring	941
15	C-N stretching in NO_2 group	828
16	C-H bending	741
17	Aromatic C-H bending	701

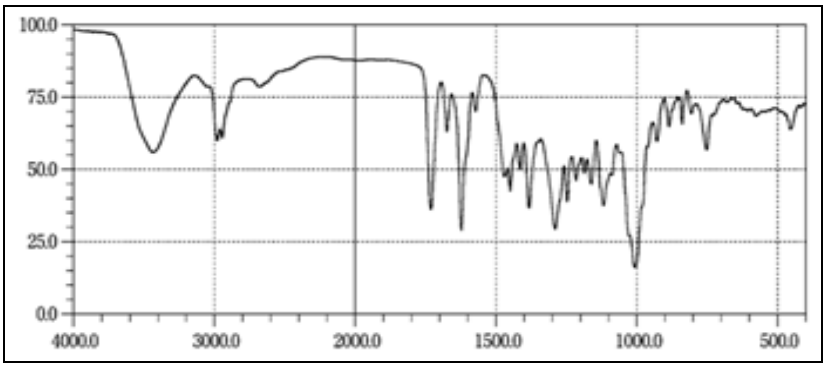

FIG. 2: FTIR SPECTRUM OF BENIDIPINE (API)+POLYETHYLENE GLYCOL 400

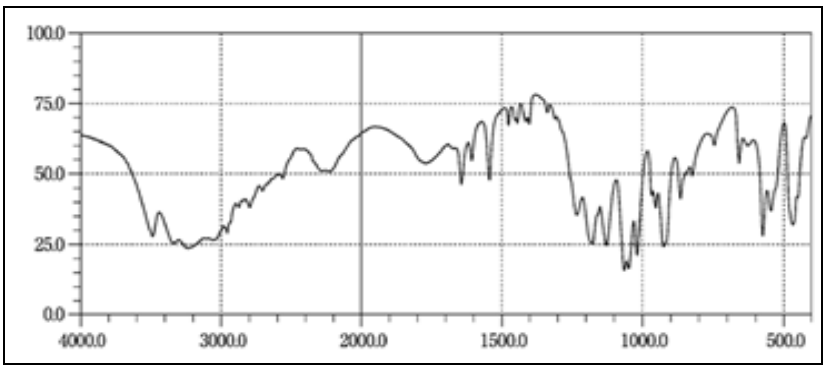

FIG. 3: FTIR SPECTRUM OF BENIDIPINE (API)+ HPMC K-100

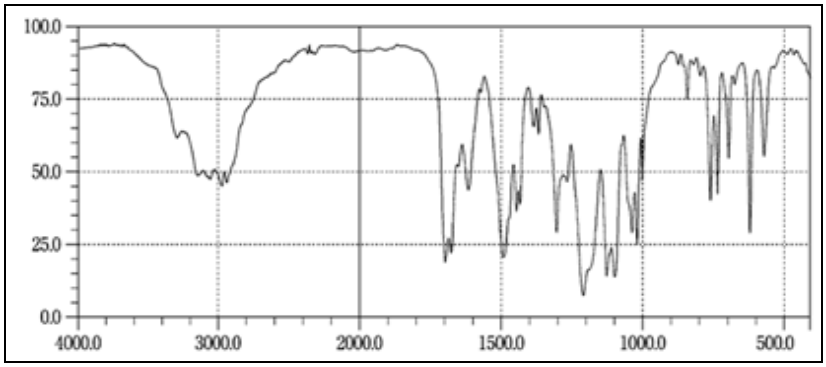

FIG. 4: FTIR SPECTRUM OF BENIDIPINE (API) + TWEEN 20

Benidipine (API) +CMC FTIR Spectra:

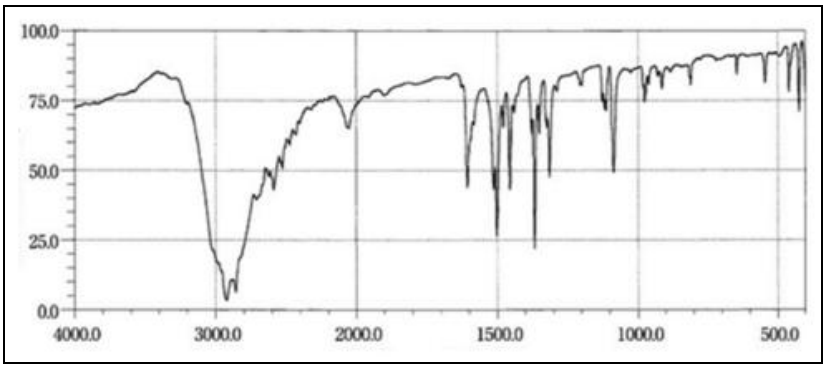

FIG. 5: FTIR SPECTRUM OF BENIDIPINE (API) + CMC

The interaction studies of drug with polymers suggests no incompatibility. Benidipine shows retention of basic characteristics as N-H stretch at3356.4 cm^{-1}, =C-H (alkene aromatic) at 2654.3 cm^{-1}, C-H (alkane stretching) at 2897.4 cm^{-1},O-H (carboxylic acid) at 2659.7, 2438.7 cm^{-1}, C=O Stretch (ester) at 1656.4, 1522.65 cm-1 and N-O Stretch at 1531.3, 1495.4 cm^{-1} as shown in FTIR of drug and excipients. The typical FTIR curves shown in **Fig. 2-4.**

Identification of Standard Drug by UV Spectroscopy (λmax): UV spectrum of benidipine sample showed characteristic UV absorption pattern with λmax at 237 nm.

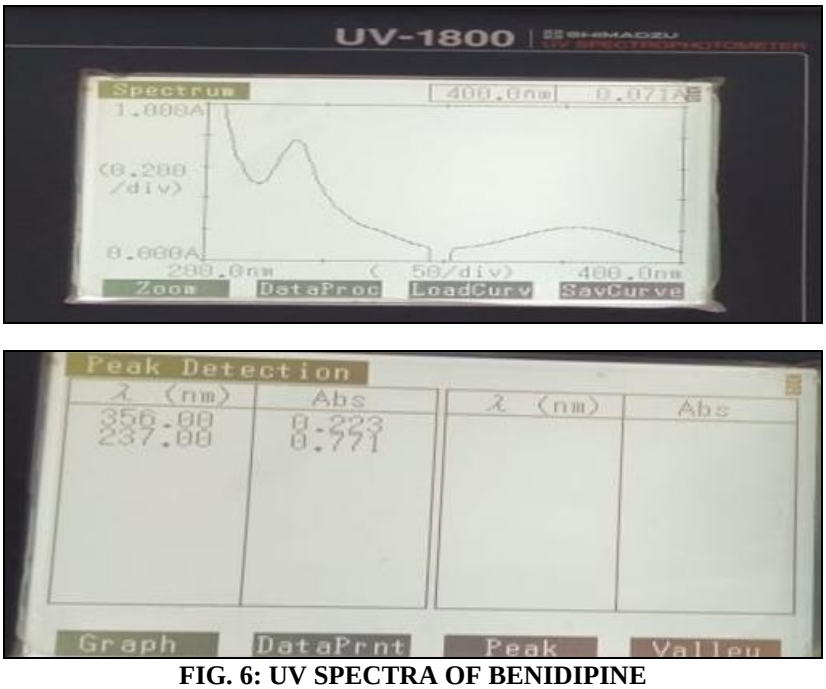

FIG. 6: UV SPECTRA OF BENIDIPINE

Formulation of Transdermal Patches: Various excipients were utilized in the formulation of transdermal patches (F1-F12) as shown in below **Table 2.**

TABLE 2: COMPOSITION OF TRANSDERMAL PATCHES

Components	F1	F2	F3	F4	F5	F6
Benidipine (mg)	250	250	250	250	250	250
HPMC K-100 (mg)	400	500	400	600	600	600
CMC (mg)	400	250	100	100	250	400
PEG -400 (ml)	0.8	0.8	0.8	0.8	0.8	0.8
Tween 20 (ml)	0.2	0.2	0.2	0.2	0.2	0.2
DMSO (ml)	0.7	0.7	0.7	0.7	0.7	0.7

Methanol: DCM (ml)	1:1	1:1	1:1	1:1	1:1	1:1
Components	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Benidipine (mg)	250	250	250	250	250	250
HPMC K-100 (mg)	500	500	500	400	500	500
CMC (mg)	250	250	250	250	100	400
PEG -400 (ml)	0.8	0.8	0.8	0.8	0.8	0.8
Tween 20 (ml)	0.2	0.2	0.2	0.2	0.2	0.2
DMSO(ml)	0.7	0.7	0.7	0.7	0.7	0.7
Methanol: DCM (ml)	1:1	1:1	1:1	1:1	1:1	1:1

Preparation of Mixture: The drug benidipine (250mg) was dissolved in 40ml of solvent mixture of methanol: dichloromethane in beaker 'A'. In beaker 'B' PEG-400, Tween 20 HPMC K-100, and CMC were dissolved in 10ml of same solvent mixture (Methanol: Dichloromethane 1:1) to get a transparent solution. Then contents of both beakers were mixed and stirred well by mechanical stirrer for 20 minutes. The air bubbles were removed with the help of ultra-sonicator. Tween 20 used as surfactant.

Casting and Drying of Films: Above mixture was poured into petri dishes, which were pretreated with silicone emulsion. These petri-dish were kept in closed box so as to control the evaporation of organic solvents used. The control of evaporation was necessary for uniform drying of films. The drying was carried out at room temperature for at least 8 –12 hours. Then the films were cut into small patches of diameter 2.5 cm. Approx 12 patches developed in one batch, each patch contain approx 16mg drug.

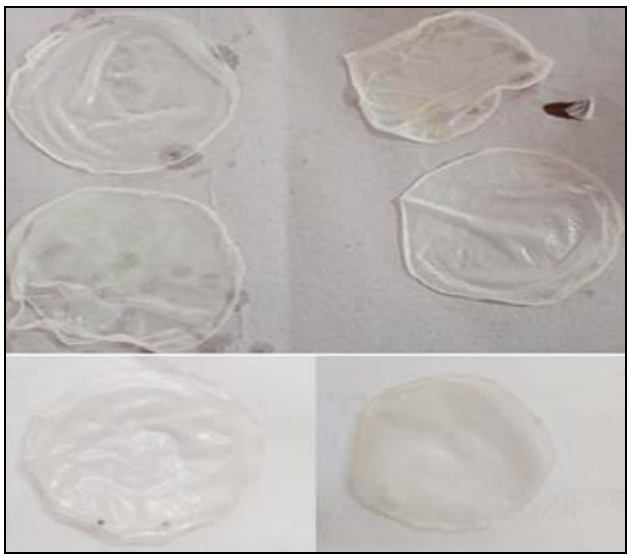

FIG. 7: FLOW DIAGRAM OF FORMULATION OF TRANSDERMAL PATCHES

Evaluation of Transdermal Patches: Twelve formulations (F1–F12) of transdermal patches were evaluated for key physicochemical parameters including thickness, weight variation, drug content uniformity, flatness, folding endurance, tensile strength, and moisture content. The results demonstrate that all formulations fell within acceptable ranges for transdermal systems, although observable variations reflect differences in polymer composition and plasticizer concentration.

Thickness and Weight: The thickness of the patches ranged from 0.247 mm (F7) to 0.329 mm (F8), indicating moderate variability across formulations. Weight values showed a corresponding trend, varying between 1000 mg (F7) and 1200 mg (F2). These variations are likely due to differences in polymer ratios and solution viscosity during casting. However, the low standard deviations suggest good uniformity within each batch.

Drug Content Uniformity: Drug content ranged from 96.25% (F1) to 97.53% (F3), demonstrating excellent uniformity across all formulations. The slight variations observed may be attributed to differences in solubilization efficiency and drug

distribution during matrix formation. Overall, all formulations met typical drug content criteria (≥95%), indicating successful incorporation of the active ingredient.

Flatness: Flatness values ranged from 92.26% (F4 and F5) to 96.62% (F1). Formulations with lower flatness likely contain higher amounts of hydrophilic polymers, which may induce slight shrinkage upon drying. However, all values remained within acceptable limits, showing minimal curvature and good structural stability.

Folding Endurance: Folding endurance values varied widely from 158 (F12) to 215 (F7). Higher endurance indicates greater flexibility and better mechanical stability, likely linked to optimized plasticizer content. F7 demonstrated the highest flexibility, which may enhance patient handling and patch durability during application.

Tensile Strength: Tensile strength ranged between 0.58 kg/cm² (F2) and 0.86 kg/cm² (F7). Formulations with higher tensile strength (F4, F7, F9) suggest stronger polymeric networks capable of withstanding mechanical stress. The combination of high tensile strength and high folding endurance in F7 indicates a well-balanced mechanical profile.

Moisture Content: Moisture content varied from 4.58% (F1) to 9.1% (F2). Formulations with higher moisture content may incorporate more hydrophilic excipients, increasing the potential for microbial growth or reduced patch stability. F1 exhibited the lowest moisture retention, which may enhance stability during storage. All moisture content levels, however, remained under 10%, which is generally acceptable to avoid brittleness or excessive softness.

TABLE 3: EVALUATION OF TRANSDERMAL PATCHES (F1-F12)

Form.	Thickness (mm)	Weight (mg)	Drug content (%)	Flatness (%)	Folding endurance (No. of folds)	Tensile strength (kg/cm^2)	Moisture content (%)
F1	0.268±0.015	1180±0.33	96.25±0.38	96.62±0.84	201± 1.67	0.64± 0.16	4.58± 0.46
F2	0.321±0.045	1200±0.16	97.46 ±0.84	94.36±1.08	172± 1.52	0.58± 0.19	9.1± 0.34
F3	0.288±0.019	1100±0.12	97.53 ±0.31	93.74±1.27	167± 1.43	0.72± 0.26	7.32± 0.29
F4	0.315±0.027	1150±0.27	97.34 ±0.20	92.26±1.34	197± 1.54	0.81± 0.34	6.51± 0.15
F5	0.284±0.029	1050±0.18	96.58 ±0.23	92.26±1.34	182± 2.19	0.71± 0.29	8.2± 0.13
F6	0.293±0.023	1140±0.16	96.82 ±0.64	96.38±0.65	170± 2.10	0.72± 0.17	7.25± 0.65
F7	0.247±0.029	1000±0.23	97.34 ±0.10	93.25±1.38	215± 1.74	0.86± 0.14	7.54± 0.23
F8	0.329±0.036	1148±0.32	96.62 ±0.35	94.47±1.36	172± 1.68	0.76± 0.17	7.2± 0.68
F9	0.318±0.011	1100±0.22	97.1 ±0.14	95.57±1.44	188± 1.57	0.84± 0.24	6.1± 0.29
F10	0.299±0.015	1080±0.18	97.38 ±0.19	96.38±0.82	162± 1.98	0.66± 0.22	6.21± 0.38
F11	0.322±0.018	1140±0.21	97.35 ±0.27	95.23±0.45	176± 2.47	0.59± 0.27	7.53± 0.32
F12	0.278±0.022	1052±0.31	96.4 ±0.32	93.36±1.65	158± 1.65	0.62± 0.12	6.98± 0.76

N=3

***In-vitro* Drug Release:** The *in-vitro* drug release study of formulations F1–F12 demonstrated an initial burst release during the first 2 hours, followed by a sustained and controlled release up to 48 hours. At 0.5 hours, release values ranged from 5.11% to 7.38%, with F7 showing the highest early release. By 2 hours, cumulative release reached approximately 11–14%, with F6 showing the highest value (13.50%), suggesting quicker initial hydration and polymer swelling. All formulations maintained a steady release pattern between 4 to 12 hours, with drug release reaching approximately 57–60% at 12 hours, reflecting uniform mid-phase diffusion characteristics. During the extended phase (18–48 hours), release continued gradually, reaching around 71–74% at 24 hours and 80–84% at 36 hours. After 48 hours, all formulations achieved high cumulative release values between 95.22% and 97.46%, with F5 showing the highest release (98.54%) and F1 the lowest (92.29%), while F4 formulation showed gradually increase pattern. Overall, the release behavior of all twelve formulations indicates effective sustained drug delivery over 48 hours, with minor variations attributed to differences in polymer composition and matrix permeability, F4 demonstrating the most favorable release profile, likely due to superior polymer–plasticizer interactions that enhanced matrix permeability and drug diffusion.

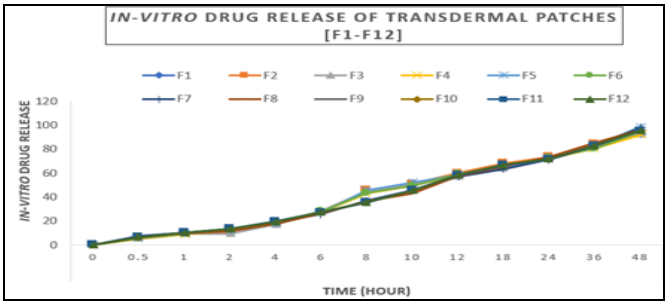

FIG. 8: GRAPHICAL REPRESENTATION OF *IN-VITRO* DRUG RELEASE OF TRANSDERMAL PATCHES [F1-F12]

***Ex-vivo* Permeation Study:** *Ex-vivo* permeation studies of formulations F1–F12 demonstrated gradual increase in cumulative drug permeation up to 48 h.

Among all formulations showed controlled release pattern, due to polymer ratio, improved vesicle stability and increased interaction with skin layers.

TABLE 4: *EX-VIVO* PERMEATION STUDY FOR F1-F12

Time (Hr.)	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	5.65±0.3	6.73±0.5	5.45±0.3	4.29±0.2	6.45±0.3	7.56±0.1
1	8.41±0.4	9.43±0.4	9.92±0.1	8.72±0.4	9.10±0.6	9.39±0.2
2	12.49±0.3	14.64±0.3	13.34±0.2	12.73±0.3	13.25±0.2	14.45±0.2
4	16.31±0.5	17.27±0.8	20.34±0.5	16.40±0.2	17.43±0.5	18.24±0.3
6	21.36±0.4	19.27±0.1	22.57±0.2	18.24±0.4	20.27±0.3	21.59±0.5
8	26.23±0.2	24.38±0.4	25.32±0.3	23.45±0.7	27.45±0.6	24.64±0.4
10	29.41±0.1	28.34±0.3	26.31±0.2	27.37±0.2	30.14±0.1	28.45±0.2
12	41.15±0.2	40.58±0.6	38.26±0.1	40.67±0.4	39.23±0.3	37.26±0.4
18	52.41±0.6	49.43±0.2	47.26±0.2	48.46±0.6	51.39±0.2	46.11±0.6
24	67.60±0.3	66.32±0.3	64.35±0.2	63.61±0.2	64.25±0.6	65.17±0.4
36	82.80±0.2	78.16±0.7	81.24±0.3	76.34±0.5	87.23±0.3	83.39±0.1
48	94.2±0.1	93.23±0.4	93.2 ±0.4	94.1 ±0.2	96.28 ±0.6	94.18 ±0.3
Time (Hr.)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	6.29±0.1	5.34±0.4	6.83±0.2	6.25±0.2	6.89±0.12	6.63±0.24
1	9.28±0.6	8.23±0.1	9.53±0.8	9.32±0.39	10.41±0.4	9.51±0.1
2	11.32±0.2	12.17±0.1	14.29±0.3	12.01±0.12	13.26±0.3	16.49±0.1
4	16.45±0.6	15.45±0.4	16.40±0.2	15.91±0.5	14.82±0.5	20.39±0.8
6	23.19±0.3	21.48±0.3	22.27±0.1	28.17±0.2	26.28±0.4	16.37±0.2
8	27.34±0.7	25.45±0.1	26.29±0.4	34.61±0.3	36.24±0.7	31.80±0.6
10	31.29±0.2	29.16±0.4	30.59±0.3	34.23±0.5	43.47±0.2	40.29±0.4
12	42.37±0.1	41.26±0.4	39.15±0.6	41.13±0.7	52.12±0.8	51.29±0.9
18	49.23±0.2	51.28±0.1	48.17±0.3	52.45±0.6	62.42±0.4	69.85±0.1
24	63.25±0.1	65.17±0.2	62.48±0.3	65.57±0.7	70.36±0.8	75.77±0.7
36	79.43±0.5	82.56±0.8	77.34±0.1	75.66±0.2	78.62±0.1	86.96±0.2
48	94.2 ±0.3	94.51 ±0.3	93.48 ±0.2	93.51 ±0.9	94.24 ±0.8	94.25 ±0.3

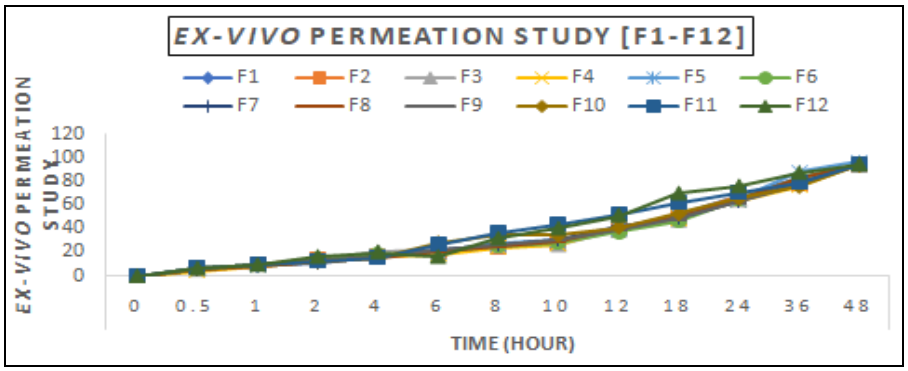

FIG. 9: *EX-VIVO* PERMEATION STUDY FOR F1-F12

Optimization of Formulation Variables *via* Central Composite Design: Central composite design was used to optimize the formulation. It was suitable for investigating the linear/quadratic response surface and constructing first/second order polynomial model using Design Expert

(version 12), thus enabling optimization of formulation with a small number of experiments run (12 runs). In this study, the two independent variables including HPMC K-100 and CMC concentration were taken which significantly influenced the observed response for drug content, moisture content, *in-vitro* drug release and *ex-vivo* drug release. Twelve formulations of transdermal patches of benidipine were prepared by solvent casting method. The polynomial equation involving the main effect and interaction factors were determined by the estimation of multiple and adjusted correlation coefficient and the predicted sum of squares generated by design experiment. The statistical validation of polynomial equation was established by ANOVA provision available in software. Thus, the determination of optimum values of variable according to the obtained experimental data was done.

TABLE 5: EXPERIMENTS AND CORRESPONDING VALUES OF CHARACTERIZATION PARAMETERS

Run	Factor 1 A: HPMC MG	Factor 2 B: CMC MG	Response 1 Drug content %	Response 2 Moisture content %	Response 3 Cumulative drug %	Response 4 *Ex-vivo* perm. Rat %
1	400	400	97.254	4.58	94.2225	94.2
2	500	250	97.46	9.1	93.4061	93.23
3	400	100	97.53	7.32	93.4916	93.2
4	600	100	97.35	6.51	94.2225	94.1
5	600	250	96.5876	8.2	97.0634	96.28
6	600	500	96.82	7.25	96.0967	94.18
7	500	250	97.34	7.54	94.2225	94.2
8	500	250	96.62	7.2	96.7589	94.51
9	500	250	97.1	6.102	94.3983	93.48
10	400	250	97.38	6.21	94.4676	93.51
11	500	100	97.35	7.53	94.2225	94.24
12	500	400	96.4	6.98	95.6374	94.25

Effect of HPMC K-100 and CMC on Drug Content Surface Response Curve: As the concentration of HPMC K-100 increases, the drug content shows a slight but consistent increase. Indicating HPMC K-100 helps maintain uniformity and stability of drug. An increase in CMC concentration also leads to an increase in drug content, and the effect appears a little stronger than HPMC K-100. CMC contributes more significantly to improving drug content, due o its better binding and dispersing ability.

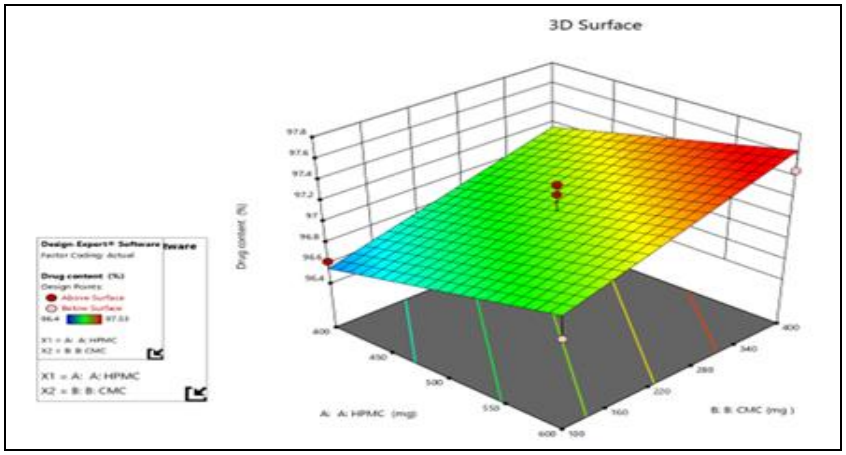

FIG. 10: RESPONSE SURFACE PLOT OF DRUG CONTENT SHOWING EFFECT OF HPMC K-100 AND CMC CONCENTRATION

TABLE 6: FACTORS OF DRUG CONTENT

Sr. no.	Factors	Values
1	Std. Dev.	0.2199
2	Mean	97.10
3	C.V. %	0.2265

4	R^2	0.7379
5	Adj. R^2	0.6797
6	Pred. R^2	0.5428
7	Adeq. precision	10.0012

TABLE 7: ANOVA TABLE FOR DRUG CONTENT

Analysis of variance table [Partial sum of squares-Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-Value**	**p- value Prob> F**	
Model	1.23	2	0.6126	12.67	0.0024	significant
A-HPMC K-100	0.4733	1	0.4733	9.79	0.0121	
B-CMC	0.7520	1	0.7520	15.55	0.0034	
Residual	0.4352	9	0.484			
Lack of Fit	0.4287	6	0.0715	32.94	0.0079	significant
Pure Error	0.0065	3				
Cor Total	1.66	11				

Effect of HPMC K-100 and CMC on Moisture Content Surface Response Curve: At higher concentration of HPMC K-100 and CMC lead to a significant increase in moisture content due to their hydrophilic nature and swelling capacity. The surface response indicates a positive correlation between polymer concentration and moisture content.

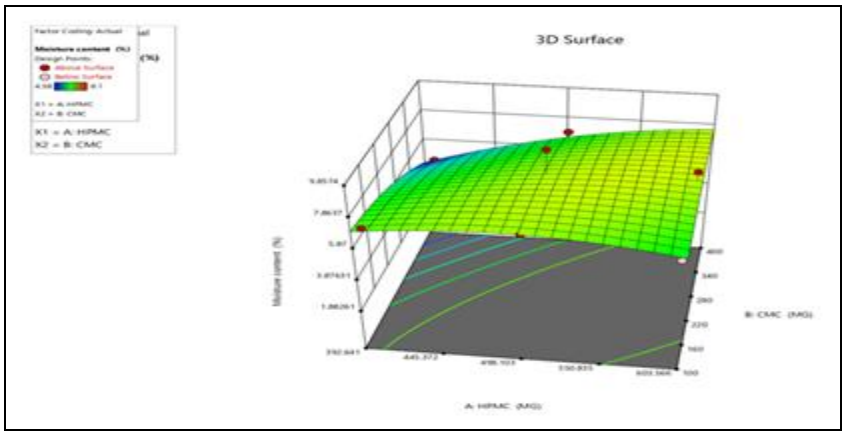

FIG. 11: RESPONSE SURFACE PLOT OF MOISTURE CONTENT SHOWING EFFECT OF HPMC K-100 AND CMC CONCENTRATION

TABLE 8: FACTORS OF MOISTURE CONTENT

Sr. no.	Factors	Values
1	Std. Dev.	0.9359
2	Mean	7.04
3	C.V. %	13.29
4	R^2	0.6281
5	Adjusted R^2	0.3182
6	Predicted R^2	0.0564
7	Adeq Precision	4.6669

TABLE 9: ANOVA TABLE FOR MOISTURE CONTENT

Analysis of variance table [Partial sum of squares-Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-Value**	**p- value Prob>F**	
Model	8.88	5	1.78	2.03	0.2075	not significant
A-HPMC K-100	2.47	1	2.47	2.82	0.1441	
B-CMC	1.08	1	1.08	1.24	0.3086	
AB	3.03	1	3.03	3.46	0.1124	
A^2	0.8370	1	0.8370	0.9555	0.3661	
B^2	0.6943	1	0.6943	0.7926	0.4076	
Residual	5.26	6	0.8760			
Lack of Fit	0.6507	3	0.2169	0.1413	0.9289	not significant
Pure Error	4.61	3	1.54			
Cor Total	14.13	11				

Effect of HPMC K-100 and CMC on Drug Release Surface Response Curve: Both HPMC K-100 and CMC reduce cumulative drug release as their concentrations increase. The retardation effect is stronger with CMC compared to HPMC K-100. This indicates that both polymers act as release-controlling agents.

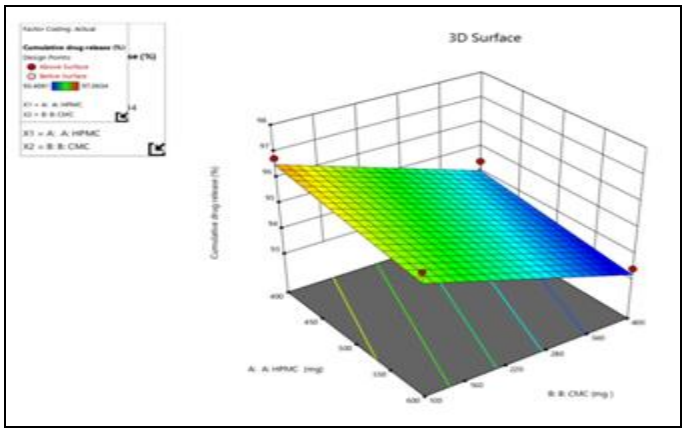

FIG. 12: RESPONSE SURFACE PLOT OF DRUG RELEASE SHOWING EFFECT OF HPMC K-100 AND CMC CONCENTRATION

TABLE 10: FACTORS OF DRUG RELEASE

Sr. no.	Factors	Values
1	Std. Dev.	0.5214
2	Mean	94.85
3	C.V. %	0.5497
4	R^2	0.8524
5	Adjusted R^2	0.8196
6	Predicted R^2	0.7688
7	Adeq Precision	13.7009

TABLE 11: ANOVA TABLE FOR DRUG RELEASE

Analysis of variance table [Partial sum of squares-Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-Value**	**p- value Prob>F**	
Model	14.13	2	7.06	25.98	0.0002	significant
A- A: HPMC K-100	1.37	1	1.37	5.03	0.0515	
B-B: CMC	12.76	1	12.76	46.93	< 0.0001	
Residual	2.45	9	0.2719			
Lack of Fit	2.45	6	0.4078			
Pure Error	0.0000	3	0.0000			
Cor Total	16.57	11				

Effect of HPMC K-100 and CMC on *Ex-vivo* Permeation Surface Response Curve:

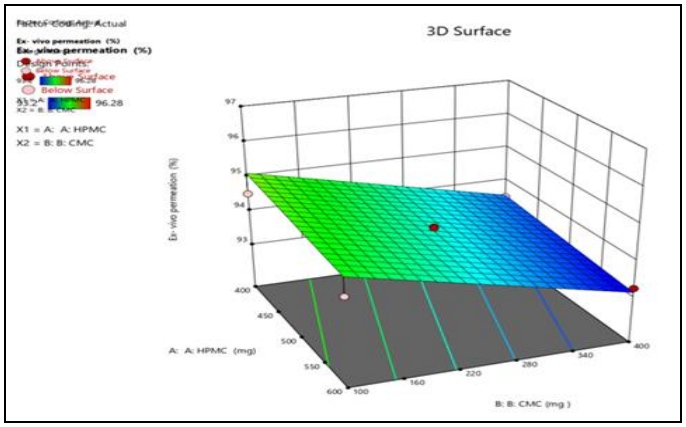

FIG. 13: RESPONSE SURFACE PLOT OF *EX-VIVO* PERMEATION SHOWING EFFECT OF HPMC K-100 AND CMC CONCENTRATION

Higher concentrations of HPMC K-100 and CMC both lead to reduced *ex-vivo* permeation, with CMC exerting a stronger retarding effect than HPMC K-100. This shows that although both polymers contribute to controlled release.

TABLE 12: FACTORS OF *EX-VIVO* PERMEATION

Sr. no.	Factors	Values
1	Std. Dev.	0.4639
2	Mean	94.12
3	C.V. %	0.4930
4	R^2	0.7341
5	Adjusted R^2	0.6750
6	Predicted R^2	0.4061
7	Adeq Precision	9.6564

TABLE 13: ANOVA TABLE FOR *EX-VIVO* PERMEATION

Analysis of variance table [Partial sum of squares-Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-Value**	**p- value Prob>F**	
Model	5.35	2	2.67	12.42	0.0026	significant
A- A: HPMC K-100	0.3307	1	0.3307	1.54	0.2465	
B-B: CMC	5.02	1	5.02	23.31	0.0009	
Residual	1.94	9	0.2152			
Lack of Fit	1.93	6	0.3211	90.03	0.0018	significant
Pure Error	0.0107	3	0.0036			
Cor Total	7.29	11				

Overlay Plot: The boxed point (centre of the yellow region) represents the predicted optimized formulation, with coded or actual values of HPMC K-100 and CMC (visible in the plot box, e.g., A = 600 mg, B = 100 mg approximately). Formulation F4 was selected as the optimized batch because its composition and responses closely matched the predicted formulation and values obtained from the Design of experiments. In Conclusion, Increasing HPMC K-100 generally enhances film-forming ability and controls drug release but may reduce moisture content and permeation at higher levels. Less CMC tends to improve swelling, hydration, and permeation. The optimum formulation (F4) lies within the yellow design space, where both polymers are balanced, ensuring high drug content, acceptable moisture level, sustained release, and improved permeation.

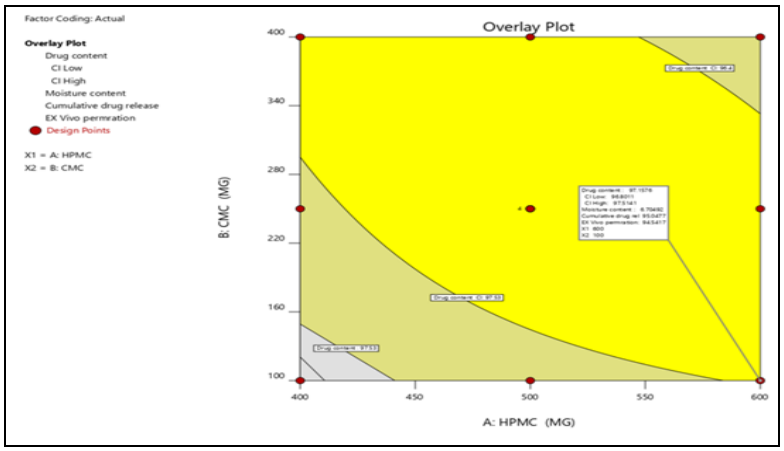

FIG. 14: AN OVERLAY PLOT OF DESIGN OF EXPERIMENT STUDY EVALUATING THE COMBINED EFFECT OF HPMC K-100 (A) AND CMC (B) CONCENTRATIONS ON VARIOUS FORMULATIONS RESPONSES

CONCLUSION: The study successfully formulated and optimized transdermal patches of benidipine using HPMC K-100 and CMC as polymeric matrices. FTIR analysis confirmed the compatibility of benidipine with all excipients, ensuring stability and suitability for patch development. Evaluation of the prepared formulations demonstrated uniform thickness, drug content, mechanical strength, and moisture stability across all batches. *In-vitro* drug release and *ex-vivo*

permeation data showed that polymer concentration significantly affected the diffusion behavior, with higher levels of HPMC K-100 and CMC producing more sustained release profiles. Optimization using Central Composite Design identified these two polymers as critical variables influencing patch performance, and the design space generated through response surface methodology enabled the selection of formulation F4 as the optimized formulation. F4 provided a desirable balance of drug content, folding endurance, tensile strength, moisture content, sustained drug release, and improved permeation. Thus, the optimized benidipine transdermal patch offers a promising alternative for prolonged antihypertensive therapy, capable of improving bioavailability, reducing dosing frequency, and enhancing patient compliance. Further *in-vivo* studies are recommended to establish therapeutic efficacy and clinical applicability.

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