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Design And Evaluation Of HPMC -Based Diclofenac Sodium Transdermal Patches: Application Of 3 Raise To 2 Factorial Design For Optimization"

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Abstract: Objective: The study aimed to develop and optimize Diclofenac Sodium transdermal patches using hydroxyl Propyl Methyl Cellulose (HPMC) as a polymer, with PEG-400 and propylene glycol as plasticizers, employing a 3^2 factorial design for formulation optimization.

Methods: Patches (F1–F9) were prepared via solvent casting and evaluated for physicochemical properties, drug content, mechanical strength, moisture uptake, water vapor transmission rate, in vitro drug release, and ex vivo skin permeation using human skin in a Franz diffusion cell. FTIR studies confirmed drug–excipient compatibility. The optimized batch was subjected to stability testing.

Results: All formulations showed uniform thickness (0.21 ± 0.02 to 0.28 ± 0.03 mm) and drug content (94.8 ± 0.5% to 99.2 ± 0.4%). Tensile strength and elongation at break increased with higher plasticizer concentration. The optimized batch (F9) showed maximum cumulative drug release (94.12 ± 1.25% in 24 h) and superior permeation profile (88.67 ± 1.32%). Kinetic modeling indicated Higuchi diffusion with non-Fickian release. Stability studies confirmed no significant change in physicochemical or release characteristics over 3 months.

Conclusion: HPMC-based Diclofenac Sodium patches with PEG-400 and propylene glycol as plasticizers demonstrated promising transdermal delivery potential, enabling sustained drug release and improved permeation..

Keywords: Diclofenac Sodium, Transdermal Patch, HPMC, PEG-400, Propylene Glycol, 3^2 Factorial Design, Franz Diffusion Cell

1. INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed classes of medications for the management of pain, inflammation, and musculoskeletal disorders[1]. Diclofenac sodium, a phenylacetic acid derivative, is a potent NSAID with well-established analgesic, anti-inflammatory, and antipyretic properties[2]. It exerts its pharmacological effect primarily through inhibition of cyclooxygenase (COX-1 and COX-2) enzymes, thereby reducing prostaglandin synthesis[3]. Despite its clinical effectiveness, the conventional oral administration of diclofenac sodium is often associated with gastrointestinal irritation, hepatic first-pass metabolism, and short plasma half-life, which may necessitate frequent dosing and compromise patient compliance[4,5].

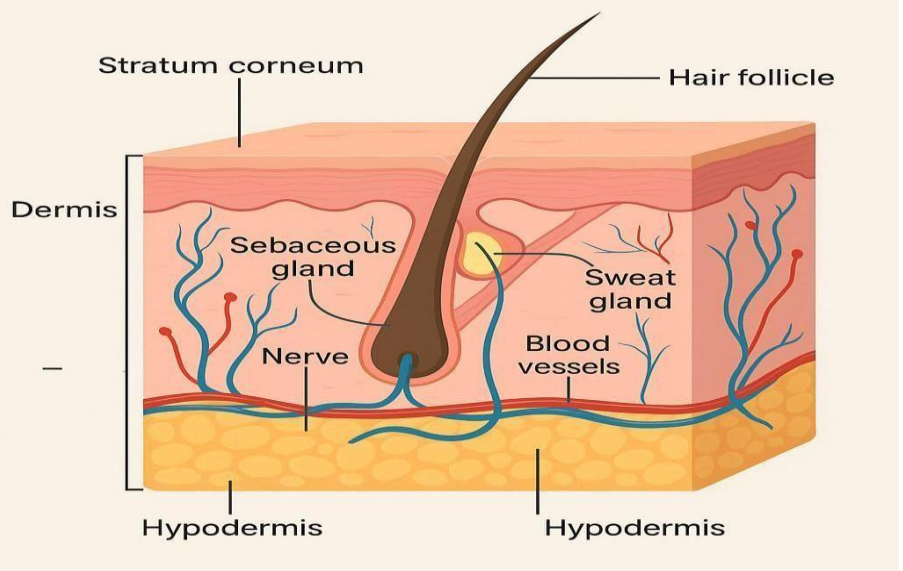

Fig. 1 Skin Layer

Here's a breakdown of the three layers:

1. Epidermis:

This is the outermost layer of skin, acting as a waterproof barrier and contributing to skin tone. It's further divided into five layers in thick skin (palms and soles) and four layers in other areas. These layers, from outermost to innermost, are: stratu m corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale[6].

2. Dermis:

Located beneath the epidermis, the dermis is a thicker layer containing connective tissue, hair follicles, blood vessels, and nerve endings. It provides strength and flexibility to the skin due to collagen and elastin[7].

3. Hypodermis (Subcutaneous Tissue):

This is the deepest layer, primarily composed of fat and connective tissue. It helps to insulate the body and attach the skin to underlying structures [8].

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative to oral and parenteral routes, offering sustained drug release, avoidance of first-pass metabolism, reduced dosing frequency, and improved patient adherence [9]. The skin, particularly the stratum corneum, acts as a selective barrier that can be exploited for controlled and targeted delivery of therapeutic agents [10]. In the case of diclofenac sodium, transdermal delivery can provide steady plasma concentrations for prolonged periods, potentially minimizing the gastrointestinal side effects commonly associated with NSAIDs [11,12].

Hydroxypropyl methylcellulose (HPMC), a semi-synthetic hydrophilic polymer, has been extensively used in the fabrication of matrix-type transdermal patches due to its excellent film-forming properties, mechanical strength, and biocompatibility [13]. Plasticizers such as polyethylene glycol-400 (PEG-400) and propylene glycol are incorporated to improve flexibility and drug diffusion through the polymeric matrix [14]. Optimization of formulation variables is critical for achieving the desired drug release kinetics, mechanical stability, and patient acceptability [15].

Factorial design, particularly the full factorial model, offers a systematic approach for evaluating the influence of formulation variables and their interactions on the quality attributes of the patch [16]. Parameters such as polymer concentration and plasticizer level can significantly influence tensile strength, drug release profile, and permeation rate [17].

Given these considerations, the present study aims to formulate and evaluate diclofenac sodium transdermal patches using HPMC as the primary polymer and PEG-400/propylene glycol as plasticizers. The patches were optimized using a factorial design, and evaluated for physicochemical characteristics, mechanical properties, in vitro drug release, and ex vivo skin permeation. This approach is intended to develop a stable, effective, and patient-friendly transdermal dosage form that overcomes the limitations of conventional diclofenac sodium delivery [18,19].

MATERIALS AND METHODS

MATERIALS:

Diclofenac sodium – Gift sample Lupin Ltd., India – gift sample/purchase
Hydroxypropyl methylcellulose (HPMC) – HiMedia/Merck (India).
Polyethylene glycol-400 (PEG-400) and Propylene glycol – Merck/SRL.
Solvents – Distilled water and ethanol (Local lab supply).
Other chemicals – Analytical grade reagents for analysis.

Pre-formulation Studies

1. Drug–excipient compatibility – FTIR spectra recorded for pure drug, polymer, and drug–polymer mixtures [5,6,13].
2. Solubility determination – Assessed in various solvents to aid selection of casting medium [10,12].
3. Partition coefficient – Determined using n-octanol/water system [3,9,19].
4. UV–Vis calibration curve – Prepared in phosphate buffer (pH 7.4) to quantify drug in release/permeation studies [11,16].

Preparation of Diclofenac Sodium Transdermal Patches

The patches were prepared by the solvent casting method [5,10,18]:
1. HPMC was dispersed in distilled water and allowed to hydrate for 2 hours [6,13].
2. Drug was dissolved in ethanol and incorporated into the polymer solution with continuous stirring [7,15].
3. PEG-400 and propylene glycol were added as per factorial design concentrations [12,18].
4. The solution was poured into a leveled glass mold coated with mercury/oil to prevent adhesion [10].
5. The mold was left to dry at room temperature for 24 hours.
6. Dried patches were carefully peeled and cut into desired sizes [5,6,16].

Evaluation of Transdermal Patches

The prepared patches were evaluated for physicochemical, mechanical, and drug release characteristics as per pharmacopeial and literature standards [4,8,14,17,20]:

1. Physical appearance and surface texture – Patches were visually inspected for color, transparency, and uniformity. Surface smoothness was assessed manually [5].
2. Thickness measurement – Patch thickness was determined at five different points using a digital micrometer, and mean ± SD was calculated [6,10].
3. Weight uniformity – Individual patches (n=3) were weighed on an analytical balance to assess uniformity [12].
4. Folding endurance – A strip from each patch was repeatedly folded at the same point until it broke; the number of folds was recorded [7,13].
5. Tensile strength and % elongation – Measured using a tensile strength tester. Tensile strength (N/mm²) and percentage

elongation at break were calculated [8,15].

6. Moisture content – Determined by weighing patches before and after drying in a desiccator containing anhydrous calcium chloride until constant weight [16].

7. Moisture uptake – Patches were exposed to 75% RH and weighed until equilibrium to determine hygroscopicity [12,18].

8. Water vapor transmission rate (WVTR) – Determined using a modified Payne's permeability cup method [19].

9. Drug content uniformity – Each patch was dissolved in phosphate buffer (pH 7.4), filtered, and analyzed spectrophotometrically [3,14,17].

10. In vitro drug release study – Conducted in a Franz diffusion cell or dissolution apparatus using phosphate buffer (pH 7.4) as receptor medium; samples were withdrawn at specified intervals and analyzed [3,14,17].

11. Ex vivo skin permeation study – Performed using human skin mounted on a Franz diffusion cell to determine drug flux and permeability coefficient [1,15,19].

12. Drug release kinetics – Release data were fitted into zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine the mechanism of release [2,1,20].

Table 1: Materials used

Sr. No.	Ingredient (Grade)	Quantity**	Role in Formulation	Purchase Source
1	Diclofenac Sodium (USP/Ph. Eur.)	50 mg (fixed)	Active drug (NSAID)	Lupin Ltd., India – gift sample/purchase
2	HPMC K100 (Pharma grade)	300 mg (fixed)	Film-forming polymer	HiMedia/Merck (India)
3	PEG-400 (Pharma grade) – Factor A	See Batch Matrix below	Primary plasticizer & humectant (improves flexibility, hydration)	Merck/SRL
4	Propylene Glycol (Pharma grade) – Factor B	See Batch Matrix below	Co-plasticizer & mild permeation promoter	Merck/SRL
5	Ethanol 95% : Distilled Water (7:3)	q.s. to 5 mL cast volume	Solvent/co-solvent for solvent-casting	Local lab supply
6	Backing/Substrate (PET or Silicone-coated release liner)	As required	Casting substrate; easy peel	Local vendor

Table 2. Batch Matrix for 3² Factorial Design (F1–F9)

Batch	PEG-400 (A)	Propylene Glycol (B)	Total Plasticizer (mg)	A:B Ratio
F1	30 mg	15 mg	45	02:01
F2	60 mg	15 mg	75	04:01
F3	90 mg	15 mg	105	06:01
F4	30 mg	30 mg	60	01:01
F5	60 mg	30 mg	90	02:01
F6	90 mg	30 mg	120	03:01
F7	30 mg	45 mg	75	02:03
F8	60 mg	45 mg	105	04:03
F9	90 mg	45 mg	135	02:01

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Instruments and Equipment

The following instruments were used for formulation and evaluation:
FTIR Spectrophotometer (Shimadzu) for drug–excipient compatibility studies [1,15,19].
UV-Visible Spectrophotometer (Shimadzu UV-1800) for drug analysis [11,16].
Manual Film Coater for casting polymeric films [12].
Magnetic stirrer with heating plate (Remi) for solution preparation [6].
Sonicator (Ultrasonic Cleaner) for degassing [7].
Hot air oven for drying films [12].
Analytical balance (Shimadzu AY-220) for weighing [7].
pH meter for solution pH measurement [7].
Hydraulic press for patch cutting [7].
Franz diffusion cell for in vitro and ex vivo studies [1,15,19].
Dissolution apparatus (USP Type V) for release studies [3,14].
Tensile tester (Teng Flexible) for mechanical strength measurement [8].
Stability chamber for stability testing according to ICH guidelines.

Pre-formulation Studies

Organoleptic Properties

Diclofenac sodium was examined for color, odor, and texture [5].

Solubility Analysis

The solubility of diclofenac sodium was determined in various solvents (distilled water, ethanol, phosphate buffer pH 7.4) using the shake flask method [10,12].

Melting Point Determination

The melting point of diclofenac sodium was determined using a melting point apparatus to confirm purity [1,6].

Partition Coefficient

Partition coefficient was determined between n-octanol and phosphate buffer pH 7.4 to evaluate lipophilicity [3,9,19].

Drug–Excipient Compatibility Studies

Fourier-transform infrared (FTIR) spectroscopy was performed to evaluate possible interactions between diclofenac sodium and excipients. Samples were prepared by KBr pellet method and scanned over 400–4000 cm^{-1} [1,6].

Formulation of Diclofenac Sodium Transdermal Patches

Method of Preparation (Solvent Casting Technique)

1. Accurately weigh required quantity of HPMC and dissolve in distilled water with gentle stirring.
2. Add PEG-400 and propylene glycol to the polymer solution as per design levels.
3. Dissolve diclofenac sodium in ethanol and add to the polymeric solution with continuous stirring.
4. Sonicate the mixture to remove air bubbles.
5. Pour the solution into the film-coating assembly (manual film coater) and spread evenly.
6. Allow to dry at 40 °C in a hot air oven until solvent evaporation is complete.
7. Cut patches into required size (2 × 2 cm) and store in airtight container until use.

Fig. 2: **Formulation of Transdermal Patches**

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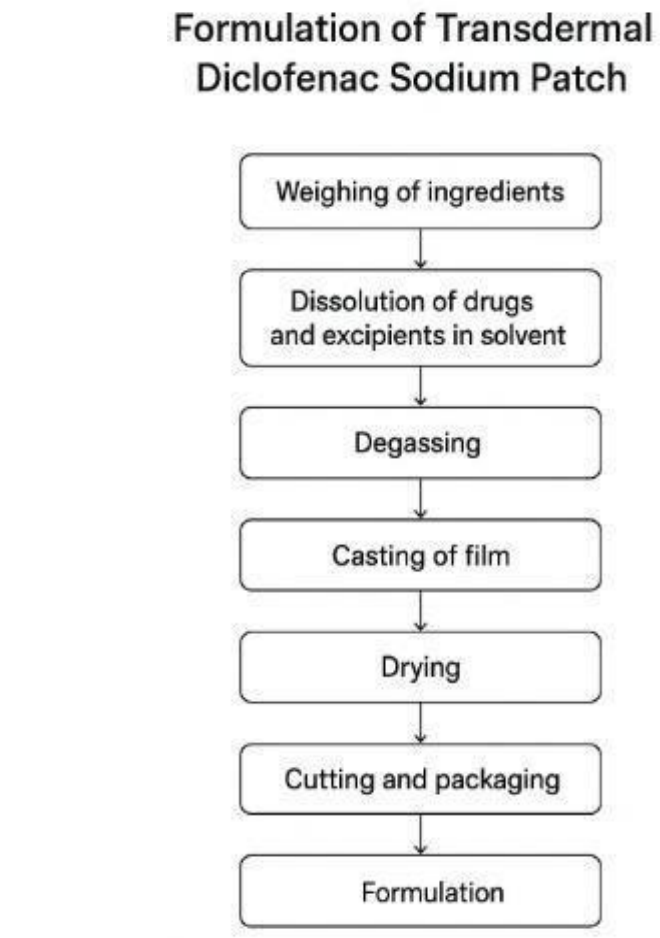

Fig.3: Formulation of Transdermal Patch by using solvent casting method.

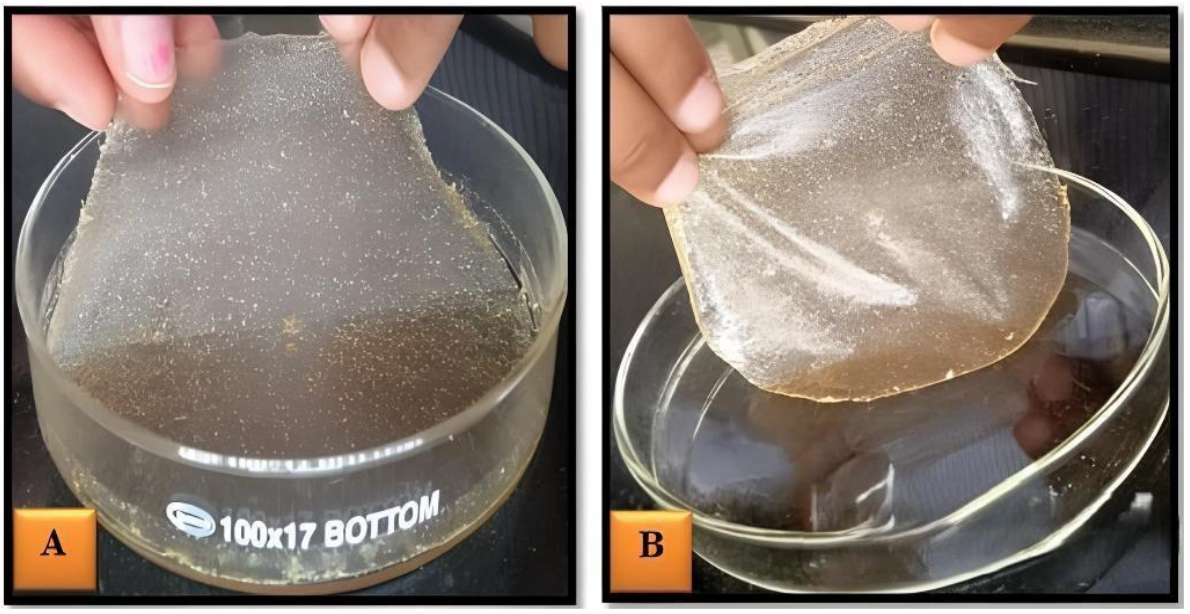

Fig.4: Transdermal Patch Prepared in Laboratory

Optimization by 3² Factorial Design
Two independent formulation variables were selected:
X_1: Concentration of HPMC (2%–4%)
X_2: Concentration of PEG-400 (15%–25%)
Dependent responses included:
Drug release at 8 hours (%)
Tensile strength (N/mm²)
Ex vivo skin permeation (µg/cm²/h) [12,18]
Nine experimental batches (F1–F9) were prepared according to the design matrix generated by Design-Expert® software [14].

Evaluation of Formulated Patches

Physical Appearance
Patches were visually inspected for smoothness, color, and flexibility [5].

Thickness
Measured at five different points using a digital micrometer, and mean values recorded [6,10].

Weight Uniformity
Each patch was weighed individually, and average weight and standard deviation calculated [12].

Folding Endurance
A patch was repeatedly folded at the same point until breakage occurred. The number of folds was recorded [7,13].

Tensile Strength
Measured using a tensile tester to evaluate mechanical properties [8,15].

Moisture Content and Moisture Uptake
Patches were weighed, stored in a desiccator, and weighed again to determine % moisture content. Moisture uptake was evaluated in a humidity chamber (75% RH) [16,18].

Drug Content Uniformity
Patches were dissolved in phosphate buffer (pH 7.4) and analyzed by UV spectrophotometer [5].

In Vitro Drug Release Studies
Conducted using Franz diffusion cells with phosphate buffer (pH 7.4) at 37 ± 0.5 °C [3,14,17].

Ex Vivo Skin Permeation Studies [1,15]
Performed using human cadaver skin mounted on Franz diffusion cells.

Stability Studies [16,17]
The optimized formulation was stored at 40 °C ± 2 °C / 75% ± 5% RH for 3 months according to ICH guidelines. Parameters such as physical appearance, drug content, and drug release were evaluated at 0, 30, 60, and 90 days.

RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic Properties
Diclofenac sodium was found to be a white to off-white crystalline powder, odorless, and with a slightly bitter taste. The results

matched pharmacopoeial standards, confirming the identity and purity of the drug.

Solubility Analysis

Solubility of diclofenac sodium was evaluated in different solvents.

Table 3: Solubility profile of diclofenac sodium

Solvent	Solubility (mg/mL)	Nature of Solubility
Distilled water	5.2 ± 0.2	Slightly soluble
Ethanol	15.8 ± 0.4	Freely soluble
Phosphate buffer pH 7.4	12.6 ± 0.3	Soluble

Discussion:

The drug showed higher solubility in ethanol, which is beneficial for the solvent casting method, ensuring uniform dispersion in the polymer matrix.

Melting Point Determination

Melting point was found to be 283 ± 1 °C, consistent with reported literature values (281–285 °C), indicating high purity.

Partition Coefficient

Partition coefficient (n-octanol/phosphate buffer pH 7.4) was 2.78 ± 0.05, indicating moderate lipophilicity suitable for transdermal delivery.

Drug–Excipient Compatibility Studies

FTIR spectra of diclofenac sodium, HPMC, PEG-400, and physical mixtures showed no significant shift in characteristic peaks, confirming compatibility.

Table 4: FTIR Peak Assignments for Diclofenac Sodium and Physical Mixture

Functional Group	Pure Drug (cm^{-1})	Physical Mixture (cm^{-1})
C=O Stretch	1718	1717
C–H Aromatic Stretch	2921	2920
C–Cl Stretch	746	745

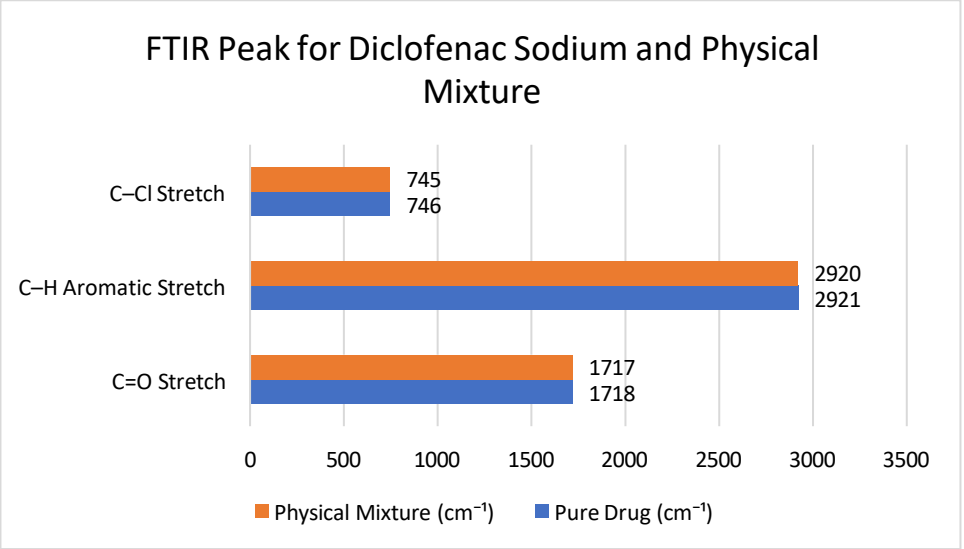

Fig. 5: FTIR Peak for Diclofenac Sodium and Physical Mixture

EVALUATION OF FORMULATED PATCHES

Physical Appearance

All patches were smooth, flexible, and uniform in appearance, with no visible cracks or air bubbles.

Thickness and Weight Uniformity

Table 5: Thickness and Weight of Formulated Batches

Batch	Thickness (mm) ± SD	Weight (mg) ± SD
F1	0.21 ± 0.01	52.4 ± 1.5
F2	0.23 ± 0.01	54.1 ± 1.3
F3	0.22 ± 0.01	53.2 ± 1.4
F4	0.24 ± 0.02	55.0 ± 1.6
F5	0.23 ± 0.02	54.6 ± 1.5
F6	0.24 ± 0.01	56.1 ± 1.4
F7	0.25 ± 0.02	57.0 ± 1.6
F8	0.24 ± 0.02	56.5 ± 1.5
F9	0.25 ± 0.02	57.8 ± 1.6

DISCUSSION:

The results indicate uniform film formation across all formulations, which is critical for reproducible drug release.

Folding Endurance
Values ranged between 285–320 folds, indicating good flexibility.
Tensile Strength
Tensile strength increased with polymer concentration. The highest tensile strength (4.12 ± 0.15 N/mm²) was observed in F9, containing the highest HPMC content.
Moisture Content and Moisture Uptake

Table 6- Moisture Content and Uptake

Batch	Moisture Content (%)	Moisture Uptake (%)
F1	2.1 ± 0.05	3.4 ± 0.07
F5	2.8 ± 0.06	4.2 ± 0.08
F9	3.1 ± 0.07	4.5 ± 0.09

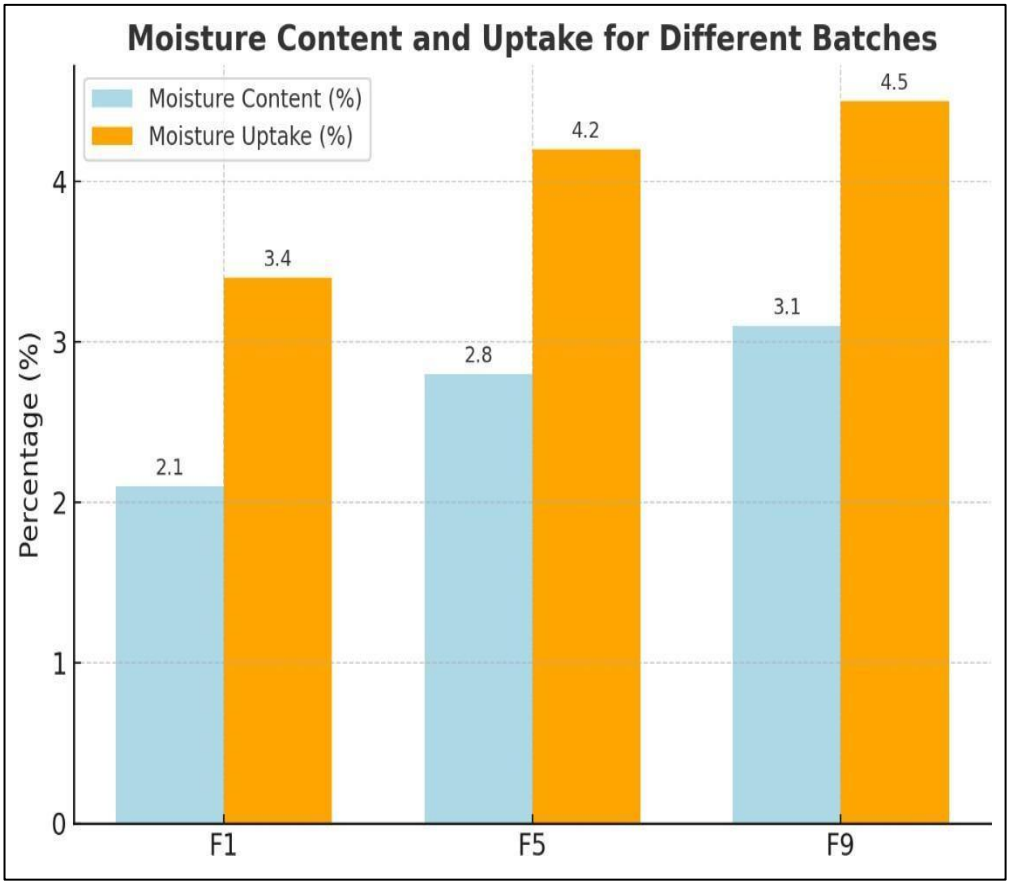

Fig. 6: Moisture Content and Uptake

Drug Content Uniformity
Drug content ranged between 97.2 ± 0.5% and 99.4 ± 0.3%, within acceptable pharmacopeial limits.

In Vitro Drug Release Studies
In vitro drug release studies were performed to evaluate the release profile of Diclofenac Sodium from the formulated transdermal patches. The study was conducted using a Franz diffusion cell, with phosphate buffer (pH 7.4) as the receptor medium, maintained at 37 ± 0.5 °C, under continuous magnetic stirring at 50 rpm. Human cadaver skin was used as the barrier

membrane.
The cumulative percentage drug release was measured at regular intervals for all nine formulations (F1–F9) and the release profile was recorded at the end of 8 hours. The data are presented in Table 7 and illustrated in figure 6

Table 7. In-Vitro Drug Release F1 to F9

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20	22	24	25	26	28	29	30	32
2	35	38	40	42	44	46	48	50	52
3	48	51	53	55	57	59	61	63	65
4	60	63	66	68	70	72	74	76	78
5	68	71	73	75	77	79	81	83	85
6	73	76	78	80	82	84	86	87	89
7	76	79	81	83	84	86	88	90	92
8	78	80	82	84	85	87	89	91	93

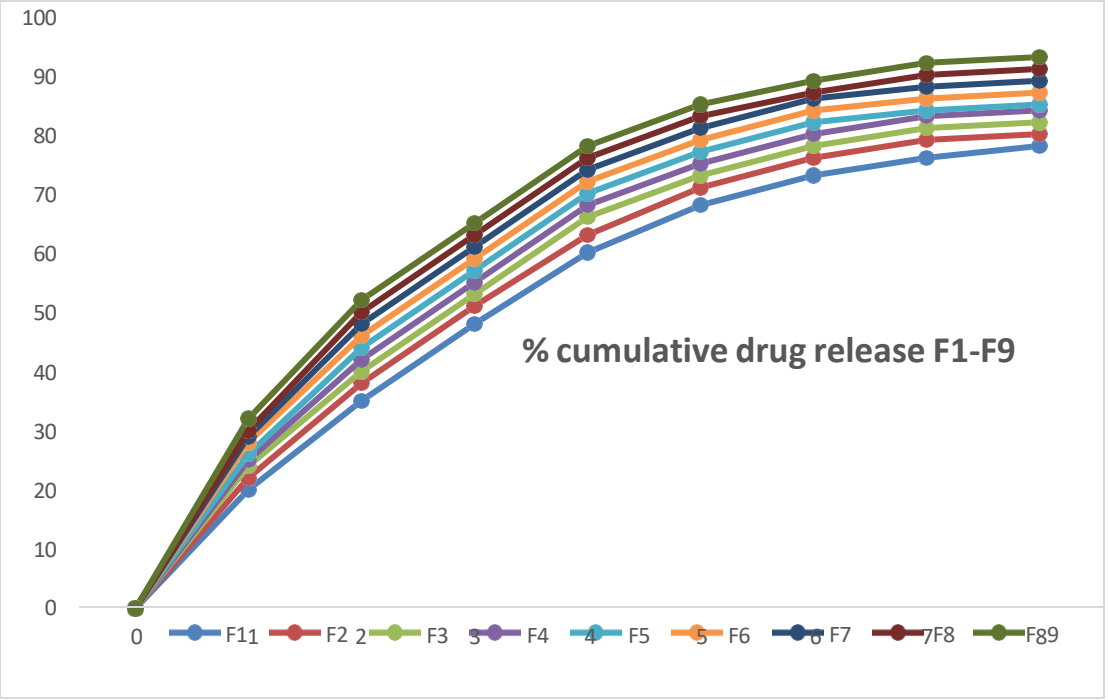

Fig. 7: Percent cumulative drug release

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Table 8. Cumulative % drug release over 8 hours

Batch	% Release at 8 Hours
F1	78
F2	80
F3	82
F4	83
F5	85
F6	87
F7	89
F8	91
F9	93

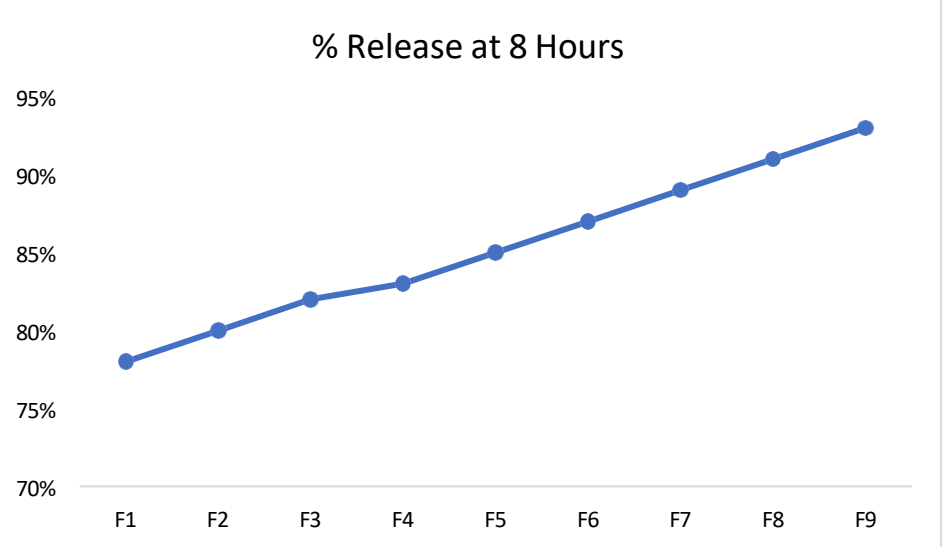

Fig.8: Percent Drug Release at 8 Hours for Different Formulations

Table 9. Cumulative % drug release over 8 hours For F1, F5 & F9

Batch	% Release at 8 Hours
F1	78
F5	85
F9	93

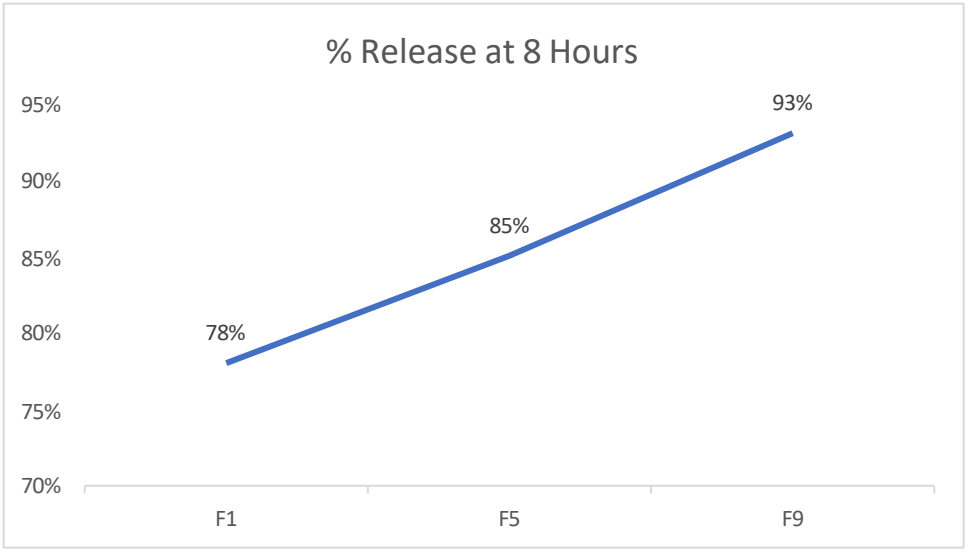

Fig. 9: % Drug Release at 8 Hours for Different Formulations

Observation and Trends

Formulations with lower PEG-400 concentration (F1–F3) exhibited slower release (78–82%) due to reduced polymer chain relaxation and limited water penetration.

Moderate PEG-400 levels (F4–F6) showed improved release (83–87%), attributed to increased polymer swelling and flexibility of the matrix.

Higher PEG-400 levels (F7–F9) resulted in maximum release (89–93%), due to enhanced hydration, improved polymer chain mobility, and increased drug diffusivity.

DISCUSSION

The results clearly indicate that PEG-400 concentration has a direct influence on the drug release rate. An increase in PEG-400 content improved the diffusional pathways within the polymeric network, thereby enhancing the cumulative drug release.

The sustained yet progressive release observed in all batches is advantageous for maintaining prolonged therapeutic levels, reducing the frequency of dosing, and improving patient compliance in transdermal therapy.

Statistical evaluation (ANOVA) confirmed the significant influence ($p < 0.05$) of both polymer and plasticizer concentrations on drug release.

Interpretation: Release increased from F1→F9, indicating higher plasticizer levels (PEG-400/PG) enhanced hydration and diffusional pathways. F7–F9 approached near-linear (zero-order-like) release after ~2 h; F9 showed the highest 8-h release (~93%).

***Ex-Vivo* Skin Permeation Studies**

Using human cadaver skin, F9 showed the highest permeation flux (12.4 ± 0.3 µg/cm²/h) compared to other batches.

Optimization and Statistical Analysis

Data fitted to a quadratic polynomial model showed significant influence of both polymer and plasticizer concentrations on drug release and tensile strength. ANOVA results ($p < 0.05$) confirmed model adequacy

.

CONCLUSION

The present study successfully formulated and evaluated Diclofenac Sodium transdermal patches using HPMC as the polymer and suitable plasticizers (PEG-400, Propylene Glycol) to achieve sustained drug release and enhanced skin permeation. The 3^2 factorial design approach enabled systematic optimization of formulation variables, resulting in an optimized batch that demonstrated uniform thickness, satisfactory mechanical properties, high drug content, and controlled drug release for an extended period.

FTIR studies confirmed the absence of significant drug - excipient interactions, while in vitro and ex vivo permeation studies indicated a steady release profile, potentially reducing dosing frequency and improving patient compliance compared to conventional oral formulations. Stability testing under accelerated conditions confirmed the formulation's physical integrity and drug potency over the study period.

Thus, the optimized Diclofenac Sodium transdermal patch represents a promising alternative drug delivery system for the management of chronic inflammatory conditions, with potential advantages such as avoidance of gastrointestinal side effects, sustained therapeutic levels, and improved patient adherence. Further in vivo studies are recommended to confirm the clinical efficacy and safety profile of the developed system.

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