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Formulation And Evaluation Of Optimized Polymer Blends For Diclofenac Diethylamine Transdermal System

Mrs. Fayeja M. Zankhwala[1]*, Mr. Amar M. Raval[2], Ms. Asefabanu M. Kushkiwala[3], Mr. Sumit P. Sarvaiya[4], Ms. Komal K. Raval[5], Ms. Nikitabahen J. Thakar[6], Ms. Shilpa V. Barjod[7]

[1]Manjushree Institute of Pharmacy, Piplaj, Gandhinagar*
[2]Sharda School of Pharmacy, Pethapur, Gandhinagar
[3]Shri B. M. Shah College of Pharmaceutical Education and Research, Modasa
[4]Indus Institute of Pharmacy and Research, Ahmedabad
[5]K. B. Raval College of Pharmacy, Shertha, Gandhinagar
[6]Vidhyadeep Institute of Pharmacy, Surat
[7]Manjushree Institute of Pharmacy, Piplaj, Gandhinagar
**Corresponding Author: Mrs. Fayeja M. Zankhwala, Email: fayejazankhwala@gmail.com*

ABSTRACT

Background: The objective of the study was to formulate and Evaluate Diclofenac Diethylamine (DDEA) transdermal patch. Transdermal systems are an enhancement in the release of drug delivery because they enable the controlled release of medication through skin absorption.

Method: This research seeks to develop Transdermal Films of Diclofenac Diethylamine employing Eudragit RL100, HPMC K100, HPMC K4M and Ethyl Cellulose. The solvents used were Ethanol, Methanol, Chloroform, and Water with PEG400 and Glycerin as the plasticizers. Patches were casted using the solvent casting method and designed using trial formulations of Eudragit RL100 with HPMC K100, HPMC K4M or Ethyl Cellulose. With the Eudragit RL100: HPMC K100 ratio, the batch was subsequently optimized with a methanolic solution of Diclofenac Diethyl amine for further refinement.

Results: The evaluation was done based on physical appearance, thickness, weight uniformity, folding endurance, and surface pH. Two formulations (Eudragit RL100: HPMC K100 and Eudragit RL100: HPMC K4M) were tested for In vitro dissolution, with the former exhibiting superior drug release, more than the latter. The percentage cumulative drug release was plotted against time. Formulation F1 demonstrated superior dissolution characteristics compared to F2, with cumulative drug release values of 45.63% and 39.98%, respectively.

Conclusion: It was concluded that it is the best choice, for fabrication of DDEA patches for the sustained release with better enhancement of DDEA.

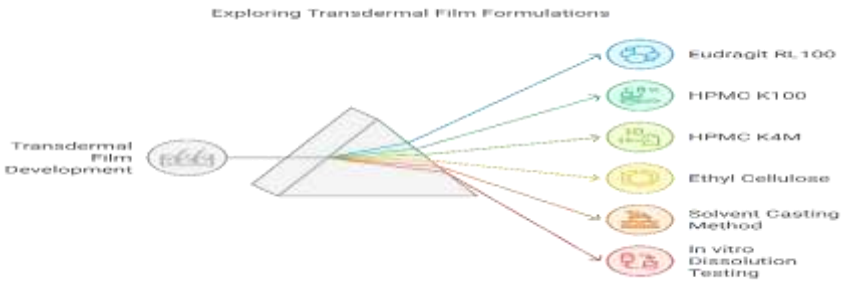

Figure 1 Graphical Abstract

Keywords: Transdermal drug delivery, Diclofenac Diethylamine patches, Solvent casting method, In vitro dissolution study, Hydroxypropylmethycellulose (HPMC), Ethyl cellulose.

INTRODUCTION

Transdermal drug delivery systems (TDDS) have emerged as a significant advancement in pharmaceutical technology, offering a non-invasive route for systemic drug administration. Unlike conventional oral or injectable routes, TDDS provides controlled and sustained drug release through the skin, bypassing first-pass metabolism and reducing gastrointestinal side effects [1]. These self-regulated dosage forms, commonly known as transdermal patches, enable precise medication delivery at predetermined rates, ensuring therapeutic efficacy and improved patient compliance [2-3].

The effectiveness of TDDS largely depends on several critical factors, including the biological properties of the skin and the physicochemical characteristics of the drug and formulation. The human skin, serving as a natural barrier, consists of three primary layers: the epidermis, dermis, and hypodermis. Among these, the stratum corneum within the epidermis acts as the principal barrier to drug permeation. Drug molecules can traverse the skin via three potential pathways: transcellular, intercellular, or appendageal (through hair follicles and sweat glands). However, the high diffusional resistance of the stratum corneum poses a significant challenge to effective transdermal drug absorption [4-7].

The selection of suitable drug candidates for TDDS requires careful consideration of molecular properties, including a molecular weight of less than 400 Da, a half-life of ≤10 hours, and a partition coefficient (Log P) ranging between -1.0 and 4.0. Additionally, ideal drugs for transdermal administration should exhibit low oral bioavailability, a narrow therapeutic index, and minimal skin irritation potential. To enhance drug permeation, permeation enhancers such as chemical agents and microneedle technologies are incorporated to disrupt lipid structures, modify intracellular proteins, or improve drug partitioning within the skin [8-11].

A well-formulated TDDS consists of multiple essential components, including a polymer matrix or drug reservoir, permeation enhancers, pressure-sensitive adhesives (PSA), and backing laminates. The polymer matrix, designed to disperse the drug in a synthetic polymer base, must be biocompatible and chemically compatible with other system components [12]. Permeation enhancers facilitate drug penetration by modifying the stratum corneum structure and should be non-toxic, non-allergenic, and pharmacologically inert. PSA ensures prolonged skin adherence, while backing laminates provide mechanical support and environmental protection [13-14]. The overall stability and efficacy of TDDS are evaluated through various parameters, including physical characterization (weight uniformity, thickness, and moisture content), chemical analysis (drug content uniformity and compatibility studies), and in vitro permeation studies using Franz diffusion cells and biological membranes [15].

Despite its numerous advantages, TDDS also presents certain limitations, such as potential skin irritation, poor permeability of hydrophilic drugs, and variability in drug absorption due to differences in skin thickness. Furthermore, the system is generally unsuitable for delivering high molecular weight drugs (>500 Da) and drugs requiring pulsatile release. Addressing these challenges requires ongoing research and technological innovations to improve formulation strategies and enhance drug permeability [16-18].

The development and optimization of TDDS rely on a thorough understanding of skin physiology, drug transport mechanisms, and formulation parameters. By overcoming existing barriers and limitations, TDDS has the potential to revolutionize drug delivery, offering a viable alternative to conventional dosage forms. Future advancements in this field may expand its applicability to a broader range of therapeutic agents, ultimately improving treatment outcomes and patient adherence [19-20].

MATERIALS AND METHODS

Diclofenac diethyl amine (DDEA) was received as a gift sample from a pharmaceutical company (details blinded for review).” The drug was characterized through the assessment of its melting point, solubility, and UV spectral analysis to ensure its suitability for transdermal formulation.

Prepare calibration curve for Diclofenac diethyl amine:

Preparation of Stock Solution: 10 mg of Diclofenac diethylamine (DDEA) was transferred into a 100 mL volumetric flask. Diluted to volume with pH 7.4 phosphate buffer to obtain a stock solution with a concentration of 100 µg/mL.

Wavelength Selection: A 1.0 mL aliquot of the stock solution was transferred into a 10 mL volumetric flask and diluted to 10 mL with phosphate buffer to obtain a final concentration of 10 µg/mL. The solution was scanned in the UV range of 400-200 nm using a UV-visible spectrophotometer to determine the maximum absorption wavelength (λmax). Based on the spectral scan, the λmax for DDEA was found to be 276 nm. Further dilutions for linearity studies were prepared from the stock solution. [8-9]

Preparation Method for Transdermal Patch: The suitable solvent (Methanol, Ethanol and Chloroform) was selected and a solvent system was prepared. Then drug (Diclofenac Diethyl amine) was dissolved in solvent system and drug employed as 660.11 mg with selected polymer (Eudragit RL100, HPMCK100, HPMCK4M and Ethyl cellulose) and plasticizer (PEG and Glycerin) was dissolved slowly with continuous stirring for 30 minutes until all the ingredients dissolve completely. The solution was kept a side for another 15 minutes to remove air bubbles. After that the solution was casted on the Petri dish (8.7 cm diameter) and dried at room temperature for 24 hours and cut into 9 cm^2 patches and kept in zip lock bag and was subjected to further evaluation.

Table 1 Formulation table of transdermal patches of Diclofenc Diethylamine

Batch code	Eudragit RL 100 (mg)	HPMC K100 (mg)	HPMC K4M (mg)	Ethyl cellulose (mg)	Methanol (ml)	Chloroform (ml)	PEG 400 (ml)	Glycerin (ml)
H1	500	500	-	-	20	30	3	0.5
H2	600	300	-	-	10	10	1	0.5
H3	600	300	-	-	20	30	0.8	0.5
H4	550	350	-	-	20	30	1	0.5
H5	650	250	-	-	10	10	1	0.5
M1	500	-	500	-	20	30	3	0.5
M2	600	-	300	-	20	30	3	0.5
M3	600	-	250	-	20	30	1	0.5
M4	600	-	200	-	10	10	1	0.5
M5	650	-	200	-	20	30	0.8	0.5
E1	500	-	-	500	20	30	3	0.5
E2	600	-	-	600	20	30	3	0.5
E3	600	-	-	600	20	30	01	0.5

DOSE CALCULATION FOR DDEA.

The diameter of petri dish was noted and area of petri-dish was calculated by following: - Diameter 8.7 cm

Radius = diameter/2 = 8.7/2= 4.35 cm

Area = $\pi r2$= 3.14×4.35×4.35 cm =59.41 cm^2 For 9 cm^2 we required 100 mg of DDEA.

So, for 59.41 cm^2 we required 660.11 mg of DEEA.

RESULTS AND DISCUSSION

Physicochemical Properties

The melting point of Diclofenac diethylamine (DDEA) was determined to be 154°C, aligning with COA specifications. Solubility analysis confirmed that DDEA is freely soluble in ethanol, methanol, and chloroform, while exhibiting partial solubility in water, crucial for optimizing formulation design. UV spectral analysis identified a maximum absorption wavelength at 267 nm.

Standard Calibration Curve of DDEA

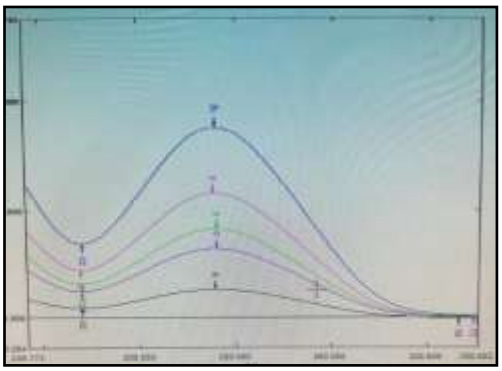

Figure 2 UV spectrum of Drug

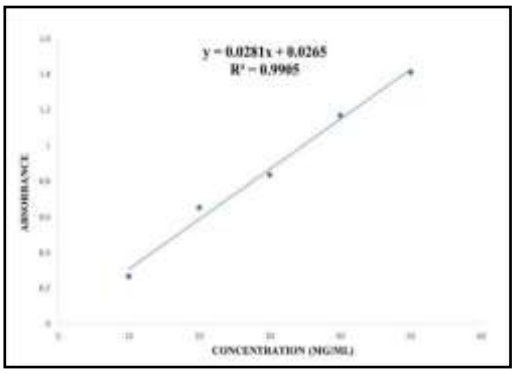

Figure 3 Calibartion curve of drug

The calibration curve for DDEA was obtained in the concentration range of 10–50 µg/mL, demonstrating good linearity with an R^2 value of 0.9905. The maximum absorbance was observed at 276 nm. UV spectrophotometric scanning in the range of 200–400 nm indicated an absorbance range of 0.268–1.412, validating the suitability of this method for drug quantification.

Evaluation of Trial Batches

The formulated batches were assessed based on physical appearance, thickness, weight uniformity, and folding endurance. Among the Eudragit RL100 and HPMC K100 batches, H2 exhibited optimal film properties with flexibility and a smooth surface, while H3 and H5 showed good film formation. H4 was opaque and rough, making it difficult to remove from the petri dish. In the Eudragit RL100 and HPMC K4M batches, M4 demonstrated the best film-forming ability with a smooth texture and high folding endurance, whereas M3 and M5 displayed good flexibility. Eudragit RL100 and Ethyl Cellulose batches E1 and E2 failed to form viable films, while E3 had an opaque, rough surface but acceptable film-forming properties.

Table 2 Formulation batches with polymer blends

Batch code	Physical appearance	Thickness (in mm)	Weight uniformity (in mg)	Folding endurance
H1	Not formed	---	---	---
H2	**Very Good**	**0.25±0.04**	**205.8±0.20**	**236±2**
H3	Good	0.26±0.02	208.36±0.35	218±4
H4	Opaque & rough	0.28±0.01	225.37±0.12	222±2
H5	Good	0.31±0.03	236.15±0.7	220±6
M1	Not formed	---	---	---
M2	Not formed	---	---	---
M3	Good	0.36±0.05	265.74±0.3	219±6
M4	**Very Good**	**0.35±0.02**	**262.06±0.2**	**226±4**
M5	Opaque	0.37±0.01	269.82±0.3	216±4
E1	Not formed	---	---	---
E2	Not formed	---	---	---

E3	Opaque & rough	0.29±0.02	222.20±0.2	204±20

Formulation with Drug (DDEA)

The optimized formulations containing DDEA were evaluated for physical parameters. Both formulations (F1 and F2) exhibited smooth surfaces with thickness values of 0.28±0.03 mm and 0.31±0.03 mm, respectively. Weight variation was observed at 292.6±0.01 mg for F1 and 329.6±0.07 mg for F2. Folding endurance values were recorded as 198±2 for F1 and 185±4 for F2. Surface pH values were within an acceptable range (6.2 for F1 and 5.98 for F2), ensuring compatibility with skin application.

Table 3 Formulation of Patches with Drug

Ingredients	**Batch F1**	**Batch F2**
DDEA	660.11 mg	660.11 mg
Eudragit RL 100	600 mg	600 mg
HPMC K 100	300 mg	-
HPMC K4M	-	200 mg
Methanol: Chloroform	1:1 mL	1:1 mL
PEG 400	1.2 mL	1.2 mL
Glycerin	0.5 mL	0.5 mL

Figure 4 F1 formulation patch

Figure 5 F2 formulation patch

Table 4 Characteristics of Drug loaded patches

Parameters	**F1**	**F2**
Physical appearance	Smooth	Smooth
Thickness (mm)	0.28±0.03	0.31±0.03
Weight variation(mg)	292.6±0.01	329.6±0.07
Folding endurance	198±2	185±4
pH	6.2	5.98
% Drug release	45.63	39.98

In Vitro Dissolution Study

Dissolution studies were performed to evaluate drug release kinetics, and the results are summarized in Table. The percentage cumulative drug release was plotted against time. Formulation F1 demonstrated superior dissolution characteristics compared to F2, with cumulative drug release values of 45.63% and 39.98%, respectively. Initially, F2 exhibited a higher drug release rate due to the viscosity-enhancing properties of HPMC K4M. However, after one hour, a decline in release rate was observed. Conversely, F1, formulated with Eudragit RL100 and HPMC K100, exhibited a more consistent and sustained release profile, making it the preferred formulation for transdermal delivery.

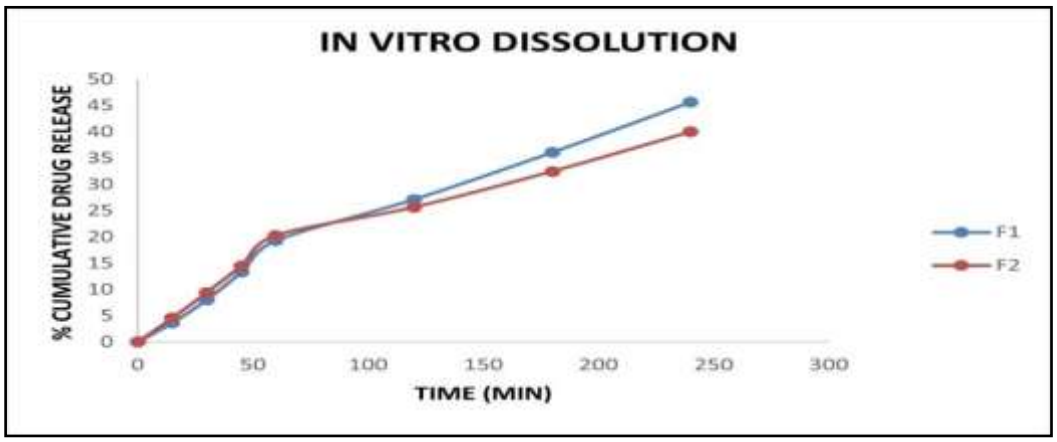

Figure 6 Invitro dissolution study

Table 5 % Cumulaive drug release

Time (min)	% Cumulative Drug Release	
	F1	F2
0	0	0
15	3.63	4.56
30	8.06	9.41
45	13.32	14.51
60	19.27	20.26
120	27.12	25.65
180	36.07	32.45
240	45.63	39.48

EVALUATION OF TRANSDERMAL PATCHES

Physical Characterization: The prepared transdermal patches were visually inspected for colour, clarity, flexibility, and surface smoothness to assess their physical appearance.

Thickness Measurement: The thickness of the patches was determined using a screw micrometer, and the results were recorded as the mean of five measurements taken from four corners and the center of each patch.

Weight Uniformity: Each formulation batch was weighed individually, and the average weight was calculated to ensure uniformity in patch composition.

Folding Endurance: The patches were cut into a standard size of 3 × 3 cm^2, and folding endurance was evaluated by repeatedly folding the films at the same location until breakage occurred. The number of folds before breaking was recorded, and the average value was calculated.

Swell-ability

Weighed 9 cm^2 patches were set in a petri dish containing 10 mL of double-distilled water to soak. At

predetermined intervals, the patch's weight upped until a steady weight was observed. The equation as follows was employed to establish the degree of swelling (S):

$$\text{Degree Swelling (S \%) of} = \frac{W_t - W_0}{W_0} \times 100$$

where S is the percent swelling, W_t is the weight of the patch at time t, and W_0 is the weight of the patch at time zero.

In Vitro Dissolution Study: Dissolution studies were performed using a Dissolution Apparatus (TDT-08L, Electrolab) with a paddle-over-disc method (USP Apparatus V). The patches (9 cm^2) were affixed to the centre of a watch glass and placed in a dissolution bucket containing 900 mL of phosphate buffer (pH 7.4). The apparatus was maintained at 37 ± 0.5°C and stirred at 50 rpm. Samples (3 mL) were withdrawn from the centre at an initial interval of 30 minutes and subsequently at 1-hour intervals. The collected samples were analysed using a UV-visible spectrophotometer to determine drug release. A graph of time versus cumulative drug release (%) was plotted, and the results were recorded.

In Vitro Drug Permeation: The developed transdermal patches were tested via an in-vitro permeation study employing a Franz diffusion cell and rat stomach skin. The skin was inserted in between the Franz diffusion cell's donor and receptor compartments. The upper portion of the skin was covered with aluminium as a support film, and the patch was mounted snugly to the stratum corneum side. Twelve millilitres of normal saline was transferred to the receptor compartment, plus a Teflon bead had been placed into it. In the course of the experiment, the ambient temperature was kept at 37 ± 5°C whilst the contents of the cell were agitated using a magnetic stirrer.

Over a span of 24-hours, 1 mL of samples were drawn through the sampling port at different vantage points in time, and each time, a uniform quantity of phosphate buffer (pH 7.4) was added. Spectrophotometric analysis was performed on the samples.

CONCLUSION

This study was focused on preparing and testing transdermal patches with Diclofenac Diethyl amine (DDEA) through the solvent casting technique. The optimally formulated test batch (F1) consisted of DDEA 660.11 mg, Eudragit RL 100 - 600 mg, HPMC K100 - 500 mg, and a solvent system in a 1:1 ratio of PEG 400 and Glycerin as plasticizers. The formulated patches were evaluated for several physicochemical properties including the patch's physical appearance, thickness (0.28±0.03 mm), weight uniformity (292.6±0.01 mg), and folding endurance (198±2). In vitro drug release studies showed that the cumulative drug release at the end of the in vitro period was 45.63% as a result of controlled drug diffusion through the polymeric matrix. The results indicate that the developed transdermal patch has acceptable physicochemical parameters and can be optimized further to improve

drug release for effective transdermal drug delivery.

Acknowledgment

The authors have no acknowledgments to declare.

Conflict of Interest

The authors declare no conflict of interest.

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