Ind. J. Pharm. Edu. Res., 2023; 57(2s):s234-s243.
https://www.ijper.org

Original Article

Formulation and Evaluation of Double-layered (Matrix and Drug-in-adhesive) Transdermal Patches of Diclofenac Diethylamine: *In vitro* and *ex vivo* Permeation Studies

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ABSTRACT

Background: The objective of this current study was to fabricate and characterize the sustained release double layered transdermal patches of Diclofenac Diethylamine using hydrophobic acrylic polymer Eudragit RL 100 and hydrophilic polymer Polyvinyl pyrrolidone K-30 in combination as first layer of matrix type patch and pressure sensitive acrylic adhesive Duro Tak 387-2510 as the second layer of drug-in-adhesive type patch to provide sustained anti-inflammatory effect. **Materials and Methods:** Solvent casting method was employed to prepare patch over the backing membrane. The double layered technique were attempted to create the desirable features of acrylic polymer and adhesive. The drug-polymers compatibility studies were examined by Infrared spectroscopy. A full-thickness excised abdominal rat skin sample was used to perform the permeation studies using Franz's Diffusion Cell. **Results:** Drug-polymers compatibility studies revealed no evidence of interaction and the formulations showed satisfactory physicochemical-mechanical characteristics. It was found that release profiles were affected by the proportion of polymer and permeation enhancer used. The optimized formulation MF3 showed maximum *in vitro* and *ex vivo* percent cumulative drug permeated i.e. 87.28 ± 3.88% and 81.95 ± 2.64% respectively, with flux 12.96 ± 0.51 μg/cm^2/h and permeability coefficient 1.09 ± 0.45 cm/h, in 24 hr. Also, the permeation studies suggested that dimethyl sulphoxide exhibit more promising results as permeation enhancer. **Conclusion:** It was concluded that an ideal Diclofenac Diethylamine double layered transdermal patch would serve as the best carrier to provide sustained effect with desirable permeation enhancement characteristics.

Keywords: Transdermal patches, Double layered technique, Hydrophobic acrylic polymer, Hydrophilic polymer, Permeation enhancer, Anti-inflammatory.

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Received: 25-04-2022;
Revised: 24-06-2022;
Accepted: 08-09-2022.

INTRODUCTION

Drugs have been delivered through the skin since primitive times. Modern delivery systems of drug are connected to the advance and novel pharmaceutical dosage forms along with the creation of new formulations in the treatment of diseases using existing drugs. Recent advancements on transdermal drug delivery systems has also attracted increasing knowledge because it provides convenient and painless self-administration; and reduces the frequency of dosage of drugs with shorter half-life, thereby increasing patient compliance.[1-3] The dosage forms are also removable in case of producing adverse effects or as when required. Transdermal delivery of lipophilic drugs is likely to be a carrier of lipophilic drugs in systemic circulation as reported by intensive research.[3]

Diclofenac is a frequently used non-steroidal anti-inflammatory drug having additional pain-relieving

DOI: 10.5530/ijper.57.2s.27

and antipyretic action.[4] It performs a crucial task in the management of musculoskeletal (MSK) problems caused by a variety of etiological illnesses, such as rheumatoid arthritis and osteoarthritis. The inhibition of enzyme namely cyclooxygenase (COX), specifically COX 1 or COX 2, is thought to be responsible for the anti-inflammatory properties which reduces prostaglandin synthesis at the inflammation site. Diethylammonium salt of Diclofenac (Diclofenac Diethylamine) is said to be utilised for topical treatments. The formulation of Voltaren® and Emulgel® contains Diclofenac Diethylamine, one of the most widely used topical treatments in Europe since 1985 for pain relief, inflammation, and muscle and joint problems. Diclofenac is usually preferred as oral formulation (100 to 150 mg with 2 to 3 divided dosage) and is capable to achieve good absorption through the gastrointestinal system, however it goes through a lot of first-pass metabolism.[4-6] Diclofenac also causes stomach irritation which can lead to nausea, bleeding, abdominal pain, and ulcers, making it unsuitable for long-term use. As a result, compared to oral diclofenac, transdermal patches have been shown to improve patient compliance.[6] Due to poor permeation of diclofenac through the skin, some conventional patches have been established less effectiveness despite the above advantages.[7]

However, the stratum corneum (a highly structured layer of the epidermis) forms a formidable layer for drug permeation. The drugs having poor permeability should be administered through it. Physical approaches such as electroporation, iontophoresis, microneedles, and sonophoresis; and chemical methods like permeation enhancers including solvents, fatty acids, surfactants, terpenes etc. are the two key tactics to increase the permeation rate through the skin.[8-9]

Dimethyl sulphoxide (DMSO) acts as a most common penetration enhancer (PE) due to its vast popularity. Drugs are frequently combined with DMSO in order to pass the skin barrier and reach systemic circulation. This aids in the reversible modification of the skin's structure for enhancing the drug permeability. DMSO facilitates safe and effective transdermal delivery of hydrophilic and lipophilic drugs to provide localized delivery.[10]

The present study aimed at developing sustained release Diclofenac Diethylamine (DDA) double layered transdermal patch using hydrophobic acrylic polymer Eudragit RL100 (ERL 100) and non-acrylic hydrophilic polymer Polyvinyl pyrrolidone (PVP K-30) in combination as first layer of matrix type patch and pressure sensitive acrylic adhesive Duro Tak 387-2510 (DT-2510) as drug-in-adhesive type patch.

MATERIALS AND METHODS

Materials

DDA was gifted by SGS Pharmaceuticals Pvt. Ltd., Roorkee, U.K.; ERL 100, PVP K-30, DMSO, Cetyl alcohol, Chloroform, di-butyl phthalate (DBP), Ethyl acetate were obtained from Merck Ltd., India; DT-2510 was from Henkel, Belgium; and 3M Scotchpak TM 9723 backing polyester membrane from 3M Food Safety Division, Healthcare Business, India.

Drug identification and drug-polymers compatibility studies

Compatibility assessment of drug and polymer involved to prepare a system is the key role in preformulation studies because the physical and chemical interaction may affect the nature, stability, bioavailability, therapeutic efficacy and safety of the drug. Therefore, FTIR spectroscopy was employed to determine the pure drug and drug-polymers compatibility studies. In this analysis, physical mixture of DDA and DDA with ERL 100, and PVP K-30 were ground in 1:1:1 ratio endorsing uniform mixing by using an agate mortar and pestle and its FTIR spectrum was acquired by using Nicolet iS50 FT-IR Spectrometer[11] and compared with reference spectrum of pure drug[12] for identifying peaks present in the region of the spectra. The sample was observed for discoloration, caking and odour formation and their FTIR spectra were also acquired after 3 weeks of storage at room temperature (RT) and compared for change in identifying peaks with that of pure drug.

Preparation of double layered transdermal patches of DDA

In first layer (matrix type) of double layered DDA transdermal patch, the solvent casting method was in in the formulation[13] by using different ratio of ERL 100 and PVP K-30, and drug DDA fixed at 100 mg. The forming solution was prepared by dissolving accurately weighed quantity of polymers followed by DDA in 10 ml of chloroform (solvent) using magnetic stirrer with Teflon coated magnetic micro bead for 2 hr following addition of DMSO and plasticizer (DBP) under 50 rpm constant stirring at RT. Continuous stirring of the mixture was done in such a manner to prevent the solvent from pre-evaporating or to keep it at a minimum. The DBP concentration was set to 10% w/w of total polymers weight because the preliminary trials proved it the optimal concentration. The polymeric solution was then poured onto the 3M Scotchpak TM 9723 backing polyester membrane using an inverted funnel placed over it to acknowledge controlled evaporation of the solvent in an oven for 4 hr at 37 ± 5°C. The detailed compositions are given in the Table 1 (Composition for matrix type layer).

Table 1: Composition of double layered transdermal patches.

Formulation Code	Composition for matrix type layer (First)					Composition for drug-in-adhesive type layer (Second)				
	Drug (DDA)	Polymers (ERL 100: PVP K-30)	Solvent (Chloroform)	Penetration Enhancer (DMSO)*	Plasticizer (DBP)*	Drug (DDA)	Cetyl alcohol#	Polymer (DT-2510)#	Solvent (Ethyl acetate)	Penetration Enhancer (DMSO)#
MF1	100 mg	9:1	10 ml	10%	40%	75 mg	2%	78%	10 ml	10%
MF2	100 mg	8:2	10 ml	10%	40%	75 mg	2%	78%	10 ml	10%
MF3	100 mg	7:3	10 ml	10%	40%	75 mg	2%	78%	10 ml	10%
MF4	100 mg	6:4	10 ml	10%	40%	75 mg	2%	78%	10 ml	10%
MF5	100 mg	5:5	10 ml	10%	40%	75 mg	2%	78%	10 ml	10%
MF6	100 mg	4:6	10 ml	10%	40%	75 mg	2%	78%	10 ml	10%
MF7	100 mg	3:7	10 ml	10%	40%	75 mg	2%	78%	10 ml	10%
MF8	100 mg	2:8	10 ml	10%	40%	75 mg	2%	78%	10 ml	10%
MF9	100 mg	1:9	10 ml	10%	40%	75 mg	2%	78%	10 ml	10%

* % w/w of polymer (total polymer weight = 500 mg).
# % w/w of polymer concentration.

Table 2: IR spectral analysis of DDA.

Wave Number Recorded (cm^{-1})	Characteristic functional group/ vibration
688.54	C-H bending Aromatic (out of plane)
744.47	C-Cl stretching
1286.43	C-N stretching aromatic
1454.23	C-C stretching aromatic
1556.45	C=C stretching aromatic
1697.24	C=O Streching Acyclic ketone carbonyl
2991.39	C=H stretching
3217.04	N-H stretching

Spreading method was used to prepare second layer (drug-in-adhesive) of double layered DDA transdermal patch.[14] A polymeric solution was prepared by using a fixed concentration of adhesive DT-2510, ethyl acetate, cetyl alcohol, and DDA with PE; and casted onto already prepared first layer (matrix type) of the patch. This polymeric solution was again permitted to assist the well-ordered evaporation of ethyl acetate in an oven for 2-3 hr at 37 ± 5°C to remove the residual organic solvents, then stored in desiccator for overnight. The detailed compositions are given in the Table 2 (Composition for drug-in-adhesive type layer).

Physico-Chemical Characterization of developed patches

Weight variation

The average weight of patches were assessed using four patches (each sized 2 cm^2) from all formulations individually with the help of an electronic analytical balance.

Thickness

The patch thickness were checked at 6 different side of each individually with the help of digital vernier caliper.

Folding endurance

The prepared patches were folded repeatedly at same angle and the folded counts (without breaking) gave folding endurance values.[15]

Percentage moisture loss

Weighed patches were kept in a desiccator holding $CaCl_2$ (anhydrous) for three days. The patches were isolated and weighed, then calculated as per formula given below under equation 1:[16]

$$\text{Percentage moisture lose} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (1)$$

Percentage moisture uptake

Accurately weighed patches were stored in a desiccator and closed for 1 day, followed by the exposure to 84% comparative humidity ($AlCl_3$ solution) in a desiccator to

achieve constant weight of the same patches; and calculated as per formula given below under equation 2:[17]

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \quad (2)$$

Drug content

Three patches of each formulation having 2 cm^2 size were cut from the formulation and weighed individually. Then the patches were engaged into 100 ml of 7.4 ± 0.1 pH phosphate buffer with continuous stirring at RT for 24 hr. The UV-visible spectrophotometer was used to measure the amount of drug present in above solution at 275 nm after filtering the solution through 0.45 µm membrane filter.[18-19]

In vitro permeation study

Franz diffusion cell (FDC) was employed to perform *in vitro* studies of drug permeation. The receptor compartment of FDC has been filled with 7.4 ± 0.1 pH phosphate buffer. The dialysis membrane was activated by keeping it into small amount of 7.4 ± 0.1 pH phosphate buffer and then cut as per required surface area. The membrane was used for release studies after being placed upon receptor compartment of FDC with a 2 cm^2, covered with donor compartment and equilibrated with receptor buffer solution for 15 min. The FDC was positioned on a hot plate assisted magnetic stirrer with continuous stirring of solution using Teflon coated magnetic bead at 37 ± 0.5°C temperature. Transdermal patches were applied on the donor compartment membrane. Each sample (1 mL) were allowed to withdraw at prefixed time intervals keeping the sink conditions always by replacing it with same amount of fresh 7.4 ± 0.1 pH phosphate buffer. After suitable dilution, the aliquots of sample were then assayed by UV-spectrophotometer at 275 nm and the % cumulative amount of drug permeated were obtained by plotted a graph against time to get permeation profile using MS Excel.[20] Additionally, the *in vitro* permeation were analyzed kinetically using mathematical models by putting the obtained values into zero order (% drug released against time), first order (log % drug released against time), Higuchi's (% drug released against square root of time) and korsmeyer pepas (% cumulative drug released against log time).

Ex vivo Permeation Study

FDC and full thickness abdominal skin of albino rats (n=3) of either sex (approximately 250 g in weight) were used to perform *ex vivo* skin permeation studies. Before beginning the study, rat skin's hair of abdominal region were removed cautiously using electric trimmer. To eliminate the tissues and other adhered cells, the dermal side was cleaned thoroughly with distilled water, followed by equilibration for 1 hr in 7.4 ± 0.1 pH phosphate buffer. The skin was then placed on previously assembled FDC with all necessary requirements exactly same as assembled for *in vitro* studies. The isolated rat skin piece should be situated between donor and receptor compartment of FDC. Each sample (1 mL) were allowed to withdraw at prefixed time intervals keeping the sink conditions always by replacing it with same quantity of fresh 7.4 ± 0.1 pH phosphate buffer. The aliquots of sample were then analyzed UV spectrophotometrically at 275 nm after filtering (to remove unwanted impurities) the solution using 0.45 μm membrane filter. Transdermal flux was measured by slop of the curve between quantity of drug permeated ($\mu g/cm^2$) vs. time (h) and permeability coefficient.[21]

Skin Irritation Study

The irritation studies were performed on hairless abdominal region of albino rat to evaluate the potential of DDA transdermal patches to cause irritation. Hairless abdominal region of albino rats (n=3) of either sex (approximately 250 g in weight) were cleaned by used to discriminate the irritation either caused by the polymers or DDA itself. Each received one patch containing DDA and one without DDA on left side and right side of rat's abdominal region externally to the skin, respectively.[22] Hairless rats were treated with the patches for 24 hr, and then they were reapplied continuously for 1 week, (day by day) to the same sites. The rat skin was then evaluated for redness, erythema, oedema, rashes and swellings to the skin.

Statement for human and animal study

Animals were handled and used according to institutional and national guidelines. Institutional Animal Ethical Committee (IAEC) established under CPCSEA (837/ac/04/CPCSEA) approved the animal's experimental protocol.

The ethical approval for animal experimental work was received by Institutional Animal Ethical Committee, IFTM University, Moradabad vide resolution no. 2021/837ac/Ph.D/15 following the OECD guidelines.

RESULTS AND DISCUSSION

In this present investigation, solvent evaporation techniques were used to develop double layered transdermal patches of DDA and studied the effect of ERL 100 and PVP K-30 (polymers of first layer); and acrylic adhesive DT-2510 (polymer of second layer) to entrap the drug in a path that sustained drug delivery may be accomplished. This technique was able to yield an optimized formulation with

optimal concentration which led to sustained drug release via this system.

Drug identification and drug-polymers compatibility studies

This was proved by the analysis of IR spectra of pure drug (Figure 1), and the mixture at 0 Time and after 3 week of storage (Figure 2) and their respective interpretation (Table 2) that all the spectra shows all the characteristic peaks of the drug at both 0 time and after 3 weeks and thus indicated no incompatibility between drug and polymers.

Physico-Chemical Characterization of developed patches

Double layered transdermal patch of DDA were fabricated by employing solvent evaporation technique. Although the polymeric solutions for both first layer and second layer were clear and transparent but the prepared patches were transparent yellowish in color (data not shown) having a smooth surface. The physio-chemical results are described in Table 3.

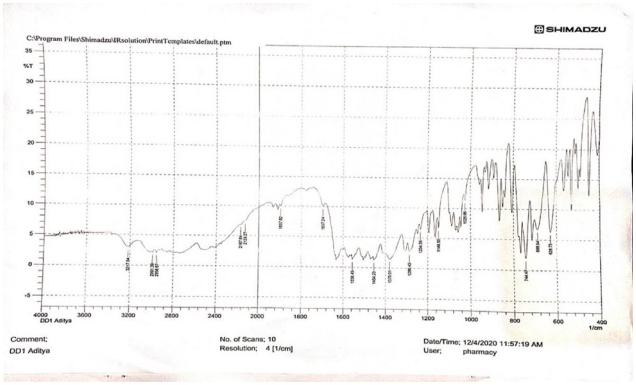

Figure 1: IR spectrum of pure DDA.

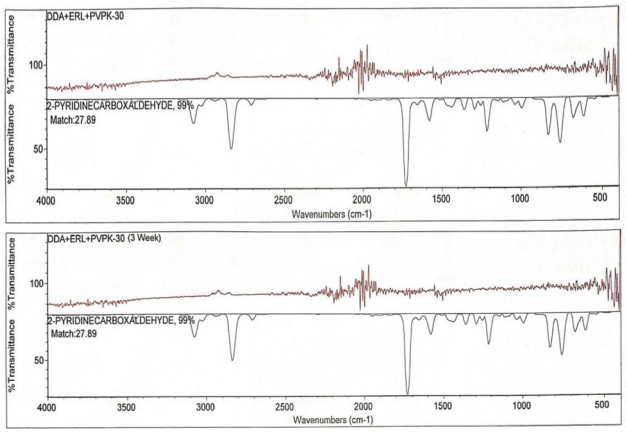

Figure 2: IR spectra of drug-polymers mixture at 0 time (upper) and after 3rd week (lower) of storage at RT.

Weight variation

It was found that formulations had uniform weight with low SD values, which indicated that patches were uniform in sized. The weight varied between 68.97 ± 0.06 mg to 74.19 ± 0.02 as shown in Table 3. The area of the patches were 2 cm^2.

Thickness

Full thickness were in ranged from 0.33 ± 0.004 mm to 0.36 ± 0.009 mm and found to be almost uniform ensured by low SD values as described in Table 3.

Folding endurance

The patches were found to be flexible, elegant and smooth even after folding 300 times (n=3), which can be recognized by the optimized concentration of DBP used as plasticizer i.e. 40% w/w. It has been noted that as the PVP K-30 concentration increased, the value of folding endurance increases as well, which may be due to the patch's higher tensile strength.[23]

Percentage moisture loss

The study revealed that as the PVP K-30 concentration rises in the patch, the moisture loss increases as well (data presented in Figure 3).

Table 3: Physico-chemical Characterization of DDA patches.

Formulation Code	Weight* (in mg)	Thickness* (in mm)	Folding Endurance*	Drug Content* (in mg)
MF1	69.38 ± 0.04	0.33 ± 0.006	>300	11.44 ± 0.942
MF2	68.97 ± 0.06	0.34 ± 0.007	>300	10.29 ± 0.687
MF3	73.34 ± 0.03	0.36 ± 0.009	>300	11.82 ± 1.122
MF4	74.19 ± 0.02	0.33 ± 0.007	>300	11.37 ± 0.829
MF5	73.92 ± 0.08	0.35 ± 0.005	>300	10.19 ± 0.158
MF6	70.20 ± 0.05	0.34 ± 0.006	>300	10.98 ± 0.787
MF7	71.27 ± 0.04	0.35 ± 0.008	>300	10.13 ± 0.982
MF8	69.89 ± 0.06	0.34 ± 0.008	>300	10.29 ± 0.238
MF9	72.21 ± 0.03	0.33 ± 0.004	>300	10.74 ± 0.401

*Values expressed as mean ± standard deviation (S.D.) in triplicate determination.

Percentage moisture uptake

According to the results, low percentage of moisture uptake were found by different formulations as presented in Figure 3. This low moisture uptake ability could be helpful in protection against microbial growth and to reduce bulkiness. Increased concentrations of the PVP K-30 were also shown to increase the percentage moisture uptake. Significant changes in characteristics such as improvement in porosity and pore size with lower crushing strength of the patches were seems to be caused by moisture uptake from the atmosphere.

The outcomes of this study clearly suggested that the moisture loss and uptake within the patches were due to the presence of PVP K-30 which has the propensity to absorb moisture from environment and bring about creation of pores thereby reducing tensile strength of prepared patches. On the other hand, DBP stabilized the intercalated complex of ERL 100 and PVP K-30 present in the formulation, also the moisture was absent at the surface of the patches which exhibit protection to the formulations from microbial contamination and consequently decreased the bioburden.

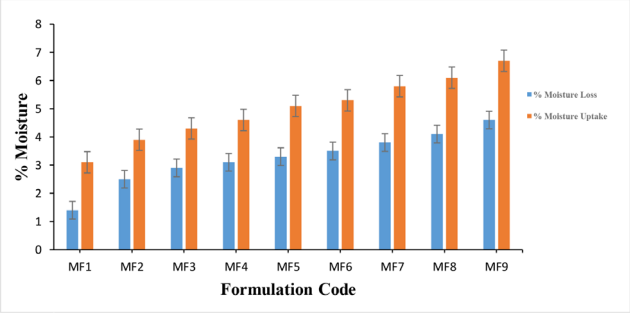

Figure 3: % Moisture loss and moisture uptake data of prepared DDA patches.

Drug content

The amount of drug in the patches were varies between 10.13 ± 0.982 mg to 11.82 ± 1.122 mg as presented in Table 3. From the outcomes, the drug was thought to be uniformly distributed throughout the patches. *In vitro* and *ex vivo* permeation studies of drug were determined based on drug amount present in respective patches.

In vitro permeation study

The resulting effects produced from *in vitro* permeation studies are depicted in Table 4 and Figure 4 shows their respective permeation curves of DDA patches.

The percentage cumulative amount were found to be different in all the nine formulations. The formulation MF3 and MF4 showed higher permeation of 87.28 ± 3.88% and 82.15 ± 3.69% respectively at 24 hr with good sustained release profile of DDA as confirmed by the curve and value of percentage drug permeated, whereas lowest permeation was observed from the formulations MF9 i.e. 46.28 ± 3.68% at 24 hr. The process of drug permeation was subjected to diffusion and concentration of polymers had a robust impact on the diffusivity. The results and graphs clearly revealed that *in vitro* drug penetration depends upon different ratio of hydrophilic and hydrophobic polymers with PE.

Table 4: *In vitro* permeation studies of DDA patches.

Time (h)	% Cumulative drug permeated*								
	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
0	0	0	0	0	0	0	0	0	0
2	9.53 ± 2.54	12.86 ± 2.14	23.13 ± 1.84	18.34 ± 2.26	13.28 ± 2.19	16.52 ± 1.45	11.32 ± 1.78	8.21 ± 2.11	4.79 ± 1.05
4	13.14 ± 2.19	21.62 ± 2.74	37.42 ± 2.98	29.13 ± 2.52	22.32 ± 2.64	26.82 ± 2.26	19.98 ± 2.95	16.73 ± 2.32	10.94 ± 1.99
6	20.19 ± 3.81	33.65 ± 2.85	48.81 ± 2.49	43.88 ± 3.54	36.20 ± 2.87	39.45 ± 2.35	27.67 ± 3.15	23.97 ± 2.64	15.2 ± 2.29
8	34.81 ± 3.25	50.67 ± 2.17	59.26 ± 3.68	51.07 ± 3.22	44.99 ± 3.24	46.71 ± 3.66	32.12 ± 3.51	29.15 ± 2.68	22.71 ± 2.66
10	46.98 ± 2.88	56.23 ± 3.69	72.19 ± 3.36	56.92 ± 2.15	57.54 ± 3.76	50.72 ± 1.97	38.03 ± 3.74	33.53 ± 2.93	31.65 ± 2.32
12	55.56 ± 2.97	62.91 ± 3.24	79.49 ± 2.99	67.22 ± 2.95	71.04 ± 2.83	57.44 ± 2.11	45.88 ± 3.25	39.45 ± 3.15	37.04 ± 3.65
24	66.22 ± 3.12	77.68 ± 2.97	87.28 ± 3.88	82.15 ± 3.69	79.60 ± 3.48	73.89 ± 3.71	59.45 ± 2.28	54.85 ± 3.12	46.28 ± 3.68

*Values expressed as mean ± S.D. in triplicate determination.

The results clearly indicated that on increasing the PVP K-30 to ERL 100 ratio from 9:1 in MF1 to 7:3 through 8:3 in MF2, permeation were increased from 66.22 ± 3.12% in MF1, to 87.28 ± 3.88% in MF3 through 77.68 ± 2.97% in MF2.

On further increasing the ratio from 7:3 in MF3 to 1:9 in MF9 through 6:4, 5:5, 4:6, 3:7 and 2:8 in MF4, MF5, MF6, MF7 and MF8 respectively, there was a fall in drug permeation. It might be possible that the fall in drug permeation may be attributed to the decreased porosity of the formulation as a result of decreased PVP K-30 amount with respect to ERL 100.

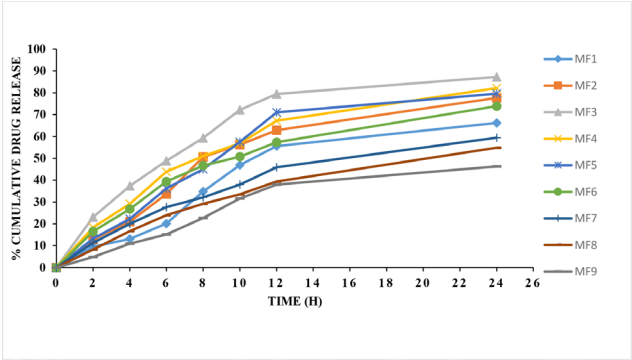

Figure 4: *In vitro* permeation studies of DDA patches.

The release/ permeation data were good fitted into zero order equation with R^2 values ranging from 0.8068 to 0.9297. Except the formulation MF9, release exponent values (n) range between 0.8389 and 0.9323 were demonstrated that the release pattern follows an anomalous delivery mechanism, as presented in Table 5.

Ex vivo permeation study

Ex vivo permeation studies of the optimized formulations are presented in Table 6 and their respective permeation curves have been shown in Figure 5. The polymer concentrations were exhibited significant impact on permeation rate of DDA. The drug permeated from the optimized formulations MF3 and MF4 with different ratio of PVP K-30 and ERL 100 in first layer; and definite concentration of DT-2510 in second layer, of double layered DDA transdermal patch was found to be 81.95 ± 2.64% and 69.61 ± 3.58%, respectively at the 24 hr of permeation. No burst release of drug were found during initial time of permeation study due to the uniform distribution of DDA in polymeric system. The sustained release drug delivery systems would be ideal if the system possibly accomplish slow drug release profile over a longer time period. Also, if the system is meant to deliver a burst release pattern, the

Table 5: ***In vitro*** **release kinetic of DDA patches.**

Parameter	Formulations								
	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
Zero order	0.8927	0.8747	0.8068	0.8679	0.8688	0.872	0.9098	0.9297	0.902
First order	0.9376	0.9632	0.9359	0.9785	0.9409	0.9689	0.9672	0.9772	0.9321
Higuchi	0.9328	0.9345	0.9337	0.9301	0.9364	0.9311	0.9258	0.9267	0.9395
Peppas	0.9737	0.9716	0.9495	0.9615	0.9785	0.969	0.9738	0.9807	0.9525
n value	0.9323	0.9102	0.8389	0.7724	0.9297	0.8227	0.8589	0.9042	1.3365
k value	1.9191	2.2129	2.4944	2.6921	2.185	2.4062	2.0537	1.8526	1.0836

Table 6: ***Ex vivo*** **permeation study of optimized patches (MF3 and MF4).**

Time (h)	% Cumulative drug permeated*	
	MF3	MF4
0	0	0
2	12.43 ± 1.15	9.93 ± 1.45
4	21.89 ± 1.32	16.51 ± 2.19
6	29.09 ± 1.98	24.58 ± 2.07
8	41.73 ± 2.10	33.6 ± 2.45
10	50.07 ± 3.13	39.95 ± 2.91
12	62.12 ± 2.88	53.87 ± 3.84
24	81.95 ± 2.64	69.61 ± 3.58

*Values expressed as mean ± S.D. in triplicate determination.

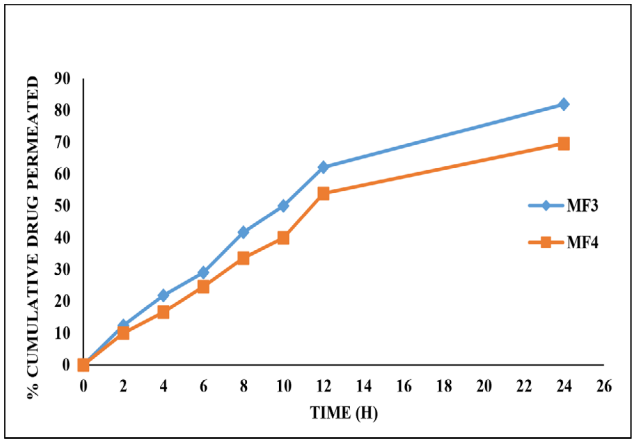

Figure 5: *Ex vivo* permeation study of optimized patches (MF3 and MF4).

Table 7: Flux and permeability coefficient of optimized patches (MF3 and MF4).

Formulation Code	Flux ($\mu g/cm^2/h$)	Permeability coefficient (cm/h)
MF3	12.96 ± 0.51	1.09 ± 0.45
MF4	11.64 ± 0.79	1.02 ± 0.24

*Values expressed as mean ± S.D. in triplicate determination.

time intervals should be adjusted accordingly to the drug release pattern.[24]

The transdermal patches were observed to remain flat and sticky to the excised skin due to the existed tendency of DT-2510, which is necessary for the continuous release of drugs. Transdermal flux is usually a measure of diffusion profile gradients at steady state. In many cases, the permeability coefficient is viewed as a factor reciting how well a drug molecule can pass the skin layer or other barriers without regard to its concentration.[25]

The polymer concentration namely ERL 100, PVP K-30 in first layer and adhesive DT-2510 in second layer significantly affected the flux and permeability coefficient of DDA from the prepared system. Formulation MF3 had the highest transdermal flux i.e. 12.96 ± 0.51 in $\mu g/cm^2/h$ and permeability coefficient 1.09 ± 0.45 cm/h, whereas formulation MF4 exhibited lower transdermal flux and permeability coefficient i.e. 11.64 ± 0.79 $\mu g/cm^2/h$, and 1.02 ± 0.24 cm/h, respectively as depicted in Table 7.

In view of these findings, it is quite apparent that morphological and structural parameters of the polymeric system have a noteworthy influence on drug permeation from the polymeric matrix. Diffusion in polymers is influenced by amorphous polymeric regions, whereas the polymer fetters and the unrestricted volume of the system govern drug diffusion.[26]

According to the results, ERL 100 inhibited the drug release from the polymer matrix in part due to its hydrophobic nature, which in turn reduced the entry of solvent into the polymeric network as well as decreased the thermodynamic activity of DDA.[27] However, the improved DDA permeation was caused by the increased porosity of the patches due to leaching effect of PVP K-30, which enlarged the porosity but decreased the diffusion of DDA to permeate into medium.[28]

Furthermore, as the simulated fluid moistens and equilibrates the isolated skin in this study, the patch comes into link with that skin part and initiate the permeation process through absorption.[29] This method leads to create a path to facilitates the drug diffusion process and also allow the permeation through polymeric system.[27,30] Therefore, to achieve the sustained release profile from this system, uniform blending of hydrophilic and hydrophobic polymer needs to be done in the appropriate ratio.

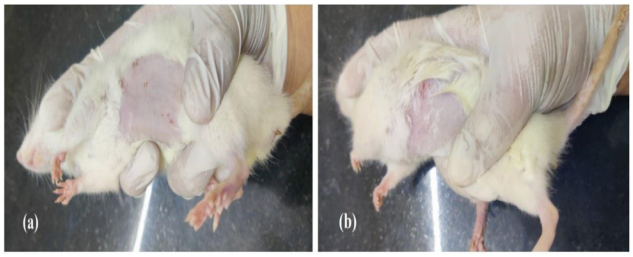

Figure 6: Skin irritation study of formulation MF3. Rat's abdominal skin region before (a) and after (b) application of patch.

Table 8: Skin irritation study data of optimized formulation MF3.

Day	Optimized formulation MF3				
	Redness	Erythema	Oedema	Rashes	Swellings
1	No	No	No	No	No
2	No	No	No	No	No
3	No	No	No	No	No
4	No	No	No	No	No
5	No	No	No	No	No
6	No	No	No	No	No
7	No	No	No	No	No

Apart from this, the effect of DMSO (used as chemical PE) on the drug release/ permeation cannot be ignored in this study. Earlier research studies revealed that DMSO was used as chemical PE. To enhance the drug penetrability, the concentration of DMSO (fixed at 10% on the basis of optimization trials) showed satisfactory result in drug permeation. It is certainly essential for PE to be used in transdermal delivery systems since which affects the SC, thus alter the therapeutic moiety to pass the drug molecules through the primary barrier of the skin and produce therapeutic outcomes.[31]

Skin irritation study

The skin irritation of optimized formulation (MF3) was determine visually after application onto the abdominal part of the albino rat for 1 week. The results for redness, erythema, oedema, rashes and swellings to the skin were found negligible as depicted in Figure 6 and Table 8. Thus, the skin irritation study suggested that the patches could be consider as safe for use.

CONCLUSION

The present research aims to elucidate the combined effect of ERL 100 (hydrophobic polymer), PVP K-30 (hydrophilic polymer), DT-2510 (acrylic adhesive) and DMSO (chemical

PE) on DDA permeation through the skin. This study showed that the double layered DDA transdermal patch containing polymers ERL 100 and PVP K-30 (as first layer) in the ratio of 7:3 with 10% w/w of DMSO; and DT-2510 (as second layer) with 10% w/w of DMSO, may attained the favorable objectives of the effective transdermal delivery systems by avoiding first pass effect, providing sustained release of drug which may avoid multiple frequency of drug administration. The double layered DDA transdermal patches were developed and assessed for various characterization and showed appropriate results in all aspects of their physico-chemical characterization, *in vitro* and *ex vivo* drug permeation, and skin irritation studies. The selected polymers revealed no incompatibility issues with DDA as confirm by drug-polymers compatibility studies. It is clear from the obtained results that the % cumulative drug permeated varied with different concentration of polymers present in the systems. It was evident that the amount of PVP K-30 and DMSO had a strong impact on increased drug permeation within each category of polymeric ratio.

According to the result, this double-layered technology (with combination of hydrophilic polymer, hydrophobic polymer and pressure sensitive adhesive) indicated that the release and permeation rate of drug may be achieved for longer period of time, which could be advantageous for managing pain associated with MSK disorders in a sustain, effective and safe manner. However in order to support its effective assertions and improved bioavailability, further pharmaco-kinetic and pharmaco-dynamic investigations needs to be conducted on animals and human beings.

ACKNOWLEDGEMENT

The authors would like to express their gratitude to honorable vice-chancellor of IFTM University, Moradabad, and Faculty of Pharmacy, IFTM University, Moradabad, for providing unstinted affectionate support and research facilities. This work is a part of work done for Ph.D. degree of IFTM University, Moradabad.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DMSO: Dimethyl sulphoxide; **PE:** Penetration enhancers; **DDA:** Diclofenac Diethyamine; **ERL 100:** Eudragit RL 100; **PVP:** Polyvinyl Pyrrolidone; **DT-2510:** Duro Tak 387-2510; **DBP:** di-butyl phthalate; **FTIR:** Fourier Transform InfraRed; **mg:** Milligram; **µm:** Micro meter; **ml:** Milli liter; **mm:** Millimeter; **nm:** Nanometer; **°C:** Degree centigrade; **hr:** Hours.

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Cite this article: Sharma A, Verma N. Formulation and Evaluation of Double-layered (Matrix and Drug-in-adhesive) Transdermal Patches of Diclofenac Diethylamine: *In vitro* and *ex vivo* Permeation Studies. Indian J of Pharmaceutical Education and Research. 2023;57(2s):s234-s243.