



## Formulation and Evaluation of Transdermal Drug Delivery System of an Anti-Inflammatory Drug using Essential Oil as Penetration Enhancer.

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### ABSTRACT:

This study focuses on formulation and evaluation of transdermal patches of Lornoxicam using various polymers to study drug release profiles and enhance transdermal drug delivery. Lornoxicam a non-steroidal anti-inflammatory drug (NSAID) is commonly associated with oral side effects such as non-compliance due to frequent dosing, gastro-intestinal irritation and ulcerogenicity. To address these limitations transdermal delivery offers a promising alternative by providing controlled drug release and improving patient compliance.

The transdermal patches were prepared using the solvent casting method with HPMC K15M and Eudragit L 100 as the polymers and lavender oil as penetration enhancer. Nine formulations (F1-F9) were developed with different polymer ratios and evaluated for various physicochemical properties including thickness, weight, folding endurance, tensile strength, moisture content and drug content. FTIR analysis confirmed the chemical compatibility between the drug and polymers while Scanning Electron Microscopy (SEM) demonstrated uniform surface morphology

In- vitro diffusion studies showed that formulation F8 comprising HPMC K15M and Eudragit L 100 in a 4:1 ratio and with 22 % of penetration enhancer provided the most sustained drug release 61.18 % over 8 hours following a non-fickian diffusion mechanism. The selected formulation F8 was subjected to stability testing for 8 weeks, the results confirmed the stability of prepared patches.

In conclusion, F8 was identified as the most promising formulation due to its superior drug release profile, mechanical properties, and stability suggesting its potential as an effective transdermal delivery system for Lornoxicam.

**Keywords:** Lornoxicam, transdermal patch, sustained release, rheumatoid arthritis.

### Introduction:

Lornoxicam is a non-steroidal anti-inflammatory medication (NSAID) frequently used to treat inflammatory conditions like rheumatoid arthritis. Although it is effective, its oral use comes with notable disadvantages such as gastrointestinal irritation, low patient adherence due to the need for frequent dosing and first-pass metabolism that diminishes its therapeutic effectiveness. To address these restrictions transdermal drug delivery systems (TDDS) have surfaced as a preferable option<sup>1</sup>. TDDS offer multiple benefits including prolonged drug release, increased bioavailability, diminished systemic side effects and improved patient adherence<sup>2</sup>. Nonetheless, the outermost layer of the skin known as the stratum corneum presents a major obstacle to drug absorption<sup>3</sup>. The application of appropriate polymers and penetration enhancers is essential for creating efficient transdermal systems. This research seeks to create and assess Lornoxicam transdermal patches utilizing hydroxypropyl methylcellulose (HPMC K15M) and Eudragit L100 as film-forming agents and incorporating lavender oil as a natural penetration enhancer<sup>4</sup>. The patches were created through the solvent casting technique and evaluated for their physicochemical characteristics, drug release kinetics and stability. The aim is to create an enhanced transdermal patch that ensures prolonged drug delivery and better therapeutic results for patients in need of extended NSAID treatment.

### Objectives:

1. To formulate transdermal patches of Lornoxicam with or without penetration enhancer.
2. To evaluate the formulated transdermal patch for various parameters.
3. To carry out the in-vitro drug diffusion studies.
4. To analyze drug release kinetics from transdermal patches.

5. To perform short term stability studies.

## Materials and Methods:

### Materials:

Lornoxicam was obtained as a complimentary sample from Yarrow Chem Products located in Mumbai, India. Hydroxypropyl methylcellulose (HPMC K15M) and Eudragit L100 which function as film-forming polymers were sourced from Ozone International and Research-Lab Fine Chem Industries Mumbai respectively. Lavender oil, used as a natural penetration enhancer was obtained from AOS Products Pvt. Ltd., located in Ghaziabad, India. Polyethylene glycol 400 (PEG 400) and dibutyl phthalate (DBP) were employed as plasticizing agents. Solvents of analytical quality such as methanol, chloroform and dichloromethane (DCM) were provided by SD Fine Chem Ltd. and Merck. All additional reagents and chemicals utilized were of analytical quality and obtained from reputable commercial suppliers.

### Drug-polymer compatibility studies:

The FTIR spectra of the selected formulation was taken and compare with spectra of pure drug and excipients. The characteristic peaks of the drug/formulation were obtained by scanning in the range of  $400\text{ cm}^{-1}$  to  $4000\text{ cm}^{-1}$  by using the spectrometer (BRUKER, ALPHAI). The samples were placed on the sample loading area and scanning was done in the range<sup>5</sup>.

### Scanning Electron Microscopy (SEM):

Transdermal patch surface morphology was examined using Scanning Electron Microscopy (SEM). To improve conductivity samples were cleaned, dried and mounted on conductive stubs before being coated in gold. To evaluate the structural characteristics of the patches, pictures were taken at different magnifications after the SEM chamber was evacuated to a high vacuum<sup>6</sup>.

### Preparation of blank transdermal patches:

Blank patches were created using various polymers such as HPMC K15M, methyl cellulose and eudragit L 100. The patches were created using the solvent casting technique. The polymers were created by combining solvents (dichloromethane, chloroform and methanol) with plasticizers like polyethylene glycol 400 and dibutyl phthalate. The solution mentioned above was transferred to a petri dish and placed in an oven at  $60^{\circ}\text{C}$  until fully dried. The patches were created using varying concentration ratios of the polymers. The dried patches were removed from the Petri dish and stored in a desiccator<sup>7</sup>.

### Preparation of drug loaded transdermal patches:

Transdermal patches were created using the solvent casting technique. The polymers were precisely measured and dissolved in appropriate solvents (dichloromethane, chloroform, and methanol). Lornoxicam was mixed with dichloromethane, chloroform and methanol (2:2:1) and subsequently incorporated into the polymeric solution. Finally, to this plasticizer was added and mixed well. The patches with penetration enhancer were incorporated into the mixture above and stirred thoroughly for even distribution. The polymer mixture containing the drug was placed in petri dishes and stored in a hot air oven at  $60^{\circ}\text{C}$  until fully dry. The dried sections were taken from the mould and kept in a desiccator. The patches were created with varying concentration ratios (Table 1).

**Table 1: Different formulations of Lornoxicam transdermal patches**

### Evaluation of transdermal patches:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lornoxicam (mg)	45.2	45.2	45.2	45.2	45.2	45.2	45.2	45.2	45.2
HPMC K15M (mg)	240	320	360	240	320	360	320	320	320
Eudragit L 100 (mg)	160	80	40	160	80	40	80	80	80
PEG 400 (% w/w)	29	29	29	-	-	-	29	29	29
Di-butyl phthalate (% w/w)	-	-	-	29	29	29	-	-	-
Lavender oil (%w/w)	11	11	11	11	11	11	-	22	33
DCM, Chloroform and methanol 2:2:1(ml)	20	20	20	20	20	20	20	20	20

### Thickness:

The thickness of all membranes was assessed with a dial micrometer (Mitutoyo, Japan) at three distinct locations on each membrane, and the average of these three measurements was calculated and reported as mean  $\pm$  SD (n=3)<sup>8</sup>.

**Folding endurance:**

A specific 2x2 cm section of the strip was cut consistently and repeatedly folded until it broke. The number of times the film was folded at the same spot, either breaking it or causing visible cracks, was used to calculate the folding endurance value<sup>9</sup>.

**Tensile strength:**

Tensile strength of patch was determined by using house-field universal testing machine. It has two load cell jaws: a fixed lower jaw and a movable upper jaw. Between these grips, films of a certain size (2 x 2 cm) were fixed, and the upper jaw moved at a speed of 100 mm/min until the patch broke. Three trails were used for this test<sup>10</sup>.

$$\text{Tensile strength } \left( \frac{\text{kg}}{\text{cm}^2} \right) = \frac{\text{Force at break (kg)}}{(\text{original width})(\text{original thickness})}$$

**Weight variation:**

The digital balance (Sartorius BS/BT, Mumbai) was used to weigh the patches, and the average weight of three readings was calculated for each patch. The values (n=3) are presented as mean  $\pm$  SD.

**Moisture content:**

The 2 cm<sup>2</sup> patches were weighed, cut, and then kept in a desiccator with CaCl<sub>2</sub> for 24 hours at 37°C. The patches were removed and reweighed after a day. This research was carried out in triplicate<sup>11</sup>.

$$\% \text{ Moisture content} = \left( \frac{\text{Initial weight} - \text{Final weight}}{\text{initial weight}} \right) \times 100$$

**Drug content:**

A transdermal film with 2 cm<sup>3</sup> sections was cut into small pieces. The patches were transferred into a 100 ml volumetric flask that contained mixtures of methanol and phosphate buffer solution (pH 6.8) (1:9). The solution was kept in rotary shaker for 24 h. After that, the contents were examined at 353 nm using a Shimadzu UV-1601 UV spectrophotometer and absorbance was measured against a suitable blank. Three duplicates of the study were conducted and the results are shown as Mean  $\pm$  SD (n = 3)<sup>12</sup>.

**Surface pH:**

A pH meter was used to measure the prepared transdermal patch's surface pH. Patch was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the patch. The values (n=3) are presented as mean  $\pm$  SD.

**Water vapour transmission (WVT) rate:**

A glass vial serves as a transmission cell and calcium chloride, which acts as a desiccant is placed inside. A film was positioned over the cell for evaluation. To maintain 84% RH, the cell was weighed and put in a desiccator that was filled with a saturated potassium chloride solution. Glass vial was removed from desiccator and reweighed after 24 h for period of 72 h. The WVT rate was determined by below mentioned formula<sup>13</sup>.

$$\text{WVT} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Area}}$$

**In-vitro drug diffusion study:**

*In-vitro* drug release from patches was determined using Franz diffusion cell with 20 ml phosphate buffer solution (pH 6.8) in receiver compartment. An egg shell membrane was clamped between the donor and receptor compartments. The media in the receptor compartment was in continuous stirring and temperature was maintained at  $37 \pm 0.5^\circ\text{C}$ . The transdermal patch was placed on the donor compartment and diffusion study was carried out for 8 h. The samples were withdrawn at different time intervals up to 8 h and replaced with an equal volume of media at each time interval. The absorbance of withdrawn samples was measured at 353 nm using UV spectrophotometer (Shimadzu UV-1601, Japan) using suitable blank. Average of three readings was taken and values are reported as mean  $\pm$  SD (n = 3).

**Preparation of egg shell membrane:**

Immerse the egg in an equal portion of 1M HCl and water for 10 minutes to dissolve the calcified shell. After the shell has dissolved, carefully crack the egg, discard the yolk and white, rinse and remove the membrane, wash it with distilled water and let it air dry (Figure 1).





without sacrificing their structural integrity by keeping the moisture content within this range. Maintaining the patch's mechanical performance and user comfort requires a proper moisture balance to avoid brittleness or excessive softness.

**Table 2: Evaluation of various physicochemical parameters of Lornoxicam transdermal patches**

Formulation Code	Thickness (mm)	Weight (mg)	Folding endurance	Moisture content (%)
F1	0.190 ± 0.005	32.55 ± 0.25	210 ± 3.25	19.87 ± 0.003
F2	0.270 ± 0.015	45.80 ± 0.40	340 ± 5.50	11.29 ± 0.040
F3	0.255 ± 0.004	35.25 ± 0.10	300 ± 4.75	15.66 ± 0.025
F4	0.280 ± 0.005	48.70 ± 0.20	320 ± 3.60	12.34 ± 0.015
F5	0.270 ± 0.010	40.35 ± 0.15	280 ± 4.20	23.15 ± 0.012
F6	0.215 ± 0.011	30.95 ± 0.35	300 ± 2.85	14.80 ± 0.020
F7	0.265 ± 0.010	32.65 ± 0.30	280 ± 5.00	19.45 ± 0.035
F8	0.270 ± 0.012	40.15 ± 0.15	350 ± 4.50	17.25 ± 0.020
F9	0.280 ± 0.005	45.00 ± 0.20	340 ± 5.25	19.50 ± 0.018

Values are in Mean ± SD (n=3)

Higher drug content in formulations with more lavender oil suggests improved drug solubility and dispersion supporting consistent and controlled drug release. The drug content in the patches ranged from  $90.15 \pm 1.10\%$  to  $94.00 \pm 1.30\%$  with all formulations exhibiting uniform drug distribution within acceptable limits.

The tensile strength values ranged from  $0.85 \pm 0.05$  to  $2.30 \pm 0.12$  kg/cm<sup>2</sup> with the highest value observed in formulation F8, indicating excellent film strength and resistance to breakage. This suggests that the combination of polymers and plasticizers used in F8 provided optimal mechanical support as patches with lower tensile strength were more prone to tearing during handling and relatively less durable. An ideal tensile strength ensures that the patch can withstand mechanical stress during storage, transportation and application without compromising drug delivery performance or user comfort.

The surface pH values were found to be between  $6.1 \pm 0.06$  and  $6.3 \pm 0.05$ , which is very close to the pH of natural skin and suggests that the patches will likely be well tolerated with minimal chance of irritation or discomfort. It is crucial to maintain this pH range in order to guarantee both skin compatibility and efficient drug penetration.

Water vapour transmission rates (WVTR) ranged from  $2.60 \pm 0.015$  to  $2.90 \pm 0.014$  g/cm<sup>2</sup>/hr  $\times 10^{-4}$ , indicating an ideal balance between permeability and moisture retention which is necessary to avoid excessive moisture accumulation or loss, maintaining the physical stability of the patch improving drug release and providing patient comfort during the application period (Table 3).

**Table 3: Evaluation of various physicochemical parameters of Lornoxicam transdermal patches**

Formulation Code	Drug content (%)	Tensile strength (Kg/cm <sup>2</sup> )	Surface pH	Water vapour transmission (gm/cm <sup>2</sup> /hr) $\times 10^{-4}$
F1	90.15 ± 1.10	0.85 ± 0.05	6.2 ± 0.05	2.80 ± 0.015
F2	92.30 ± 1.46	2.15 ± 0.15	6.3 ± 0.05	2.65 ± 0.013
F3	90.75 ± 0.75	1.50 ± 0.10	6.3 ± 0.04	2.75 ± 0.014
F4	91.40 ± 1.50	2.22 ± 0.20	6.4 ± 0.03	2.60 ± 0.015
F5	93.50 ± 0.80	1.70 ± 0.18	6.1 ± 0.06	2.90 ± 0.014
F6	90.60 ± 1.20	2.00 ± 0.25	6.3 ± 0.05	2.85 ± 0.013
F7	90.80 ± 1.00	0.95 ± 0.05	6.2 ± 0.07	2.75 ± 0.155
F8	93.40 ± 1.20	2.30 ± 0.12	6.3 ± 0.04	2.65 ± 0.014
F9	94.00 ± 1.30	2.15 ± 0.15	6.2 ± 0.04	2.70 ± 0.016

**Values are in Mean  $\pm$  SD (n=3)**

To evaluate the effectiveness of transdermal patches loaded with Lornoxicam, in-vitro drug release studies were carried out (Tables 4 & 5; Figures 5 – 7). Among formulations F1–F3, which contained 11% w/w lavender oil and were plasticized with PEG 400, formulation F2 had the best release profile, achieving  $42.18 \pm 0.78\%$  drug release at 8 hours. The reason for this was the ideal ratio of Eudragit L100 to HPMC K15M, which produced a balanced matrix that allowed for effective drug diffusion. However, F1 which had a higher content of Eudragit L100 had the lowest release ( $35.95 \pm 1.93\%$ ) most likely because of a denser matrix structure that made it harder for the drug to move around. Due mainly to a higher concentration of HPMC K15M which enhanced initial drug solubility and promoted rapid diffusion, F3 showed a burst release effect ( $89.24 \pm 0.40\%$ ).

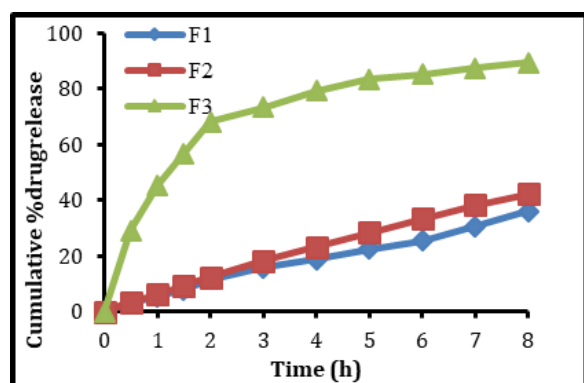
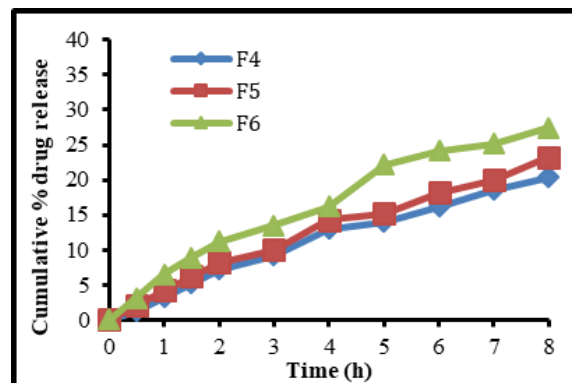
With the same concentration of lavender oil and plasticized with di-butyl phthalate, formulations F4–F6 showed noticeably slower drug release ( $20.35\text{--}27.47\%$  at 8 hours). Due to increased matrix hydrophobicity the plasticizer decreased drug diffusion while simultaneously increasing film flexibility. Films that lacked a penetration enhancer were disqualified from additional analysis due to their low drug release.

**Table 4: In-vitro drug diffusion studies from formulations F1 to F5**

Time (h)	Cumulative % drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	$3.19 \pm 0.53$	$3.45 \pm 0.21$	$29.15 \pm 1.39$	$1.19 \pm 1.85$	$2.01 \pm 2.31$
1	$5.30 \pm 0.67$	$6.14 \pm 0.34$	$45.26 \pm 0.87$	$3.15 \pm 2.18$	$4.18 \pm 2.72$
1.5	$7.86 \pm 0.24$	$9.24 \pm 0.55$	$56.83 \pm 2.78$	$5.24 \pm 2.64$	$6.14 \pm 1.42$
2	$11.52 \pm 0.41$	$12.14 \pm 0.51$	$68.12 \pm 3.16$	$7.18 \pm 0.98$	$8.18 \pm 2.09$
3	$15.76 \pm 1.13$	$18.18 \pm 1.62$	$73.16 \pm 1.57$	$9.18 \pm 1.49$	$10.02 \pm 2.50$
4	$18.74 \pm 2.92$	$23.18 \pm 2.81$	$79.24 \pm 1.61$	$12.98 \pm 3.37$	$14.24 \pm 0.73$
5	$22.40 \pm 2.07$	$28.18 \pm 3.46$	$83.26 \pm 3.68$	$13.14 \pm 5.99$	$15.21 \pm 3.99$
6	$25.42 \pm 0.81$	$33.14 \pm 1.82$	$85.18 \pm 1.63$	$16.18 \pm 3.46$	$18.14 \pm 0.94$
7	$30.49 \pm 1.19$	$38.18 \pm 0.86$	$87.41 \pm 0.79$	$18.57 \pm 2.48$	$19.98 \pm 1.82$
8	$35.95 \pm 1.93$	$42.18 \pm 0.78$	$89.24 \pm 0.40$	$20.35 \pm 0.85$	$23.25 \pm 3.79$

**Values are in Mean  $\pm$  SD (n=3)**

Formulations F7 to F9 were developed by modifying the concentration of penetration enhancer. With a lower drug release of  $31.25 \pm 1.65\%$  at 8 hours, F7 which was made without any penetration enhancer, demonstrated limited diffusion through the polymer matrix. When the penetration enhancer concentration was raised to 22% w/w in F8 the drug release significantly improved reaching  $61.18 \pm 2.27\%$ . A similar release of  $62.25 \pm 0.82\%$  was observed in F9 which contained 33% w/w penetration enhancer. This suggests that increasing the concentration beyond 22% did not significantly enhance drug permeation. These findings emphasize how crucial a penetration enhancer's presence and proper concentration are to facilitating efficient drug release. It was discovered that F2 was the most successful formulation in delivering Lornoxicam transdermally in a controlled and sustained manner.

**Figure 5: Cumulative % drug release from formulations F1 to F3****Figure 6: Cumulative % drug release from formulations F4 to F6****Table 5: In-vitro drug diffusion studies from formulations F6 to F9**

Time (h)	Cumulative % drug release			
	F6	F7	F8	F9
0	0	0	0	0
0.5	3.12 ± 1.98	3.48 ± 1.39	6.18 ± 1.74	7.11 ± 3.67
1	6.48 ± 3.68	5.24 ± 0.87	12.18 ± 1.83	13.18 ± 2.18
1.5	8.88 ± 2.22	7.47 ± 2.78	17.98 ± 0.67	18.14 ± 0.94
2	11.21 ± 1.52	9.14 ± 3.16	22.45 ± 1.30	23.04 ± 2.22
3	13.47 ± 1.89	11.47 ± 3.68	29.89 ± 0.68	29.18 ± 1.76
4	16.18 ± 0.95	15.18 ± 0.79	36.01 ± 2.18	36.14 ± 2.54
5	22.54 ± 3.59	16.47 ± 1.61	42.84 ± 2.08	43.14 ± 2.39
6	24.15 ± 2.76	19.14 ± 0.40	50.18 ± 0.34	50.24 ± 1.54
7	25.12 ± 2.65	20.14 ± 1.63	56.18 ± 0.86	57.18 ± 3.12
8	27.47 ± 3.33	22.48 ± 1.57	61.18 ± 2.27	62.25 ± 0.82

Values are in Mean ± SD (n=3)

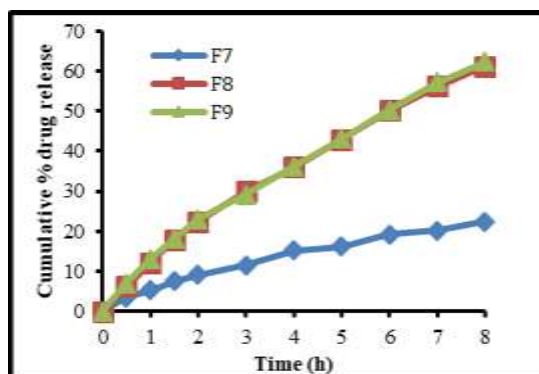


Figure 7: Cumulative % drug release from formulations F7 to F9

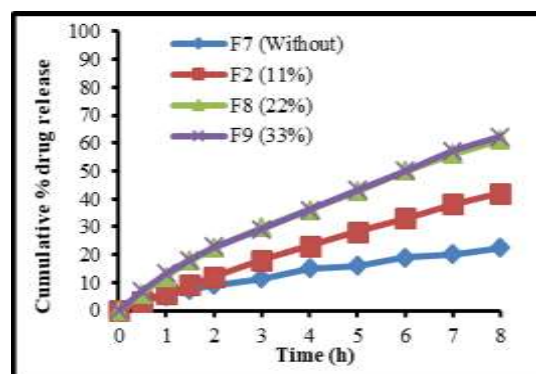


Figure 8: Cumulative % drug release of Lornoxicam with and without penetration enhancer



Figure 9: Transdermal patch of formulation F8

Table 6: Kinetics of drug release of Lornoxicam transdermal patches

Formulation Code	Regression co-efficient ( $R^2$ )			Korsmeyer's -Peppas plot 'n' values
	Zero order ( $R^2$ )	First order ( $R^2$ )	Higuchi equation ( $R^2$ )	
F1	0.993	0.975	0.995	0.830

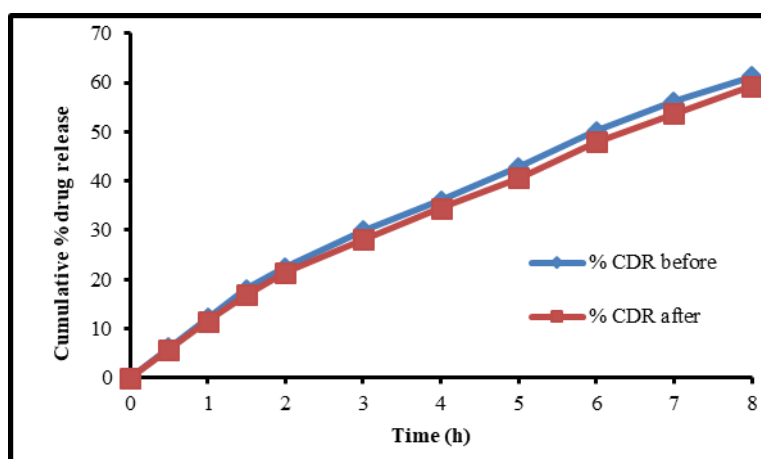
F2	0.968	0.980	0.983	0.883
F3	0.986	0.952	0.966	1.025
F4	0.992	0.991	0.945	0.815
F5	0.990	0.986	0.941	1.050
F6	0.992	0.986	0.925	1.065
F7	0.992	0.996	0.951	1.074
F8	0.953	0.950	0.993	0.885
F9	0.945	0.938	0.989	0.932

Formulations F1, F2, F8 and F9 followed Higuchi drug release model. Zero order kinetics was followed by formulations F3, F4, F5 and F6. First order kinetics was followed by formulation F7. With  $n$  values of 1.025, 1.050, 1.065 and 1.074 formulations F3, F5, F6 and F7 demonstrated Super Case II transport characteristics, where drug release was strongly impacted by polymer relaxation and erosion. Formulation F8 followed non-fickian diffusion release mechanism. In comparison to all other formulations, formulation F8 demonstrated a better release of  $61.18 \pm 2.27\%$ . The best formulation was determined to be F8 (Table 6).

Formulation F8 was tested for stability over a period of eight weeks at room temperature and at  $40 \pm 5^\circ\text{C}$  with  $75 \pm 5\%$  relative humidity (Table: 7 & Figure: 10). Formulation F8's stability and sustained use during the evaluation period were confirmed by drug content and in-vitro release studies, indicating that it is suitable for long-term storage.

**Table 7: Stability study of formulation F8: Drug content and Cumulative % drug release at 0 and 8 weeks**

Stability Study of Formulation F8	Initial	After 8 weeks
Drug content (%)	$93.40 \pm 1.20$	$92.15 \pm 0.76$
Cumulative % drug release at 8 hrs	$61.18 \pm 2.27$	$59.26 \pm 1.45$



**Figure 10: Comparison of drug release from formulation F8 before and after 8 weeks of stability testing**

## Conclusion

Lornoxicam, a potent NSAID with a short half-life and gastrointestinal side effects was selected for transdermal delivery to improve patient compliance. Solvent casting was used to create formulations (F1–F9) using HPMC K15M and Eudragit L100. In order to improve penetration lavender oil was added to F2 based on evaluation results (F7–F9). Patch surfaces were uniform as demonstrated by SEM and FTIR verified drug-excipient compatibility. Every formulation complied with acceptable physicochemical standards. The drug release from F8 was  $61.18 \pm 2.27\%$  over 8 hours and was characterized by a non-Fickian diffusion mechanism. Long-term performance was validated by stability studies. The formulation F8 was determined to be the most promising for transdermal delivery of Lornoxicam.

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