International Journal of Advances in Pharmaceutics
ISSN: 2320–4923; DOI: 10.7439/ijap
Volume 5 Issue 2 [2016]
Journal home page: http://ssjournals.com/index.php/ijap

Research Article

Formulation and *in-vitro* characterization of lornoxicam transdermal matrix patch

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Keywords:
Transdermal Drug Delivery system,
Transdermal Patch,
Lornoxicam,
Solvent Casting Method.

Abstract

Transdermal therapeutic systems are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver drug(s), through skin, at a controlled rate to systemic circulation. In the present study transdermal patches of Lornoxicam were prepared using hydrophilic polymer and hydrophobic polymer. Transdermal drug delivery system has the potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for a longer period of time, resulting in a reduction of dosing frequency, improved bioavailability, and decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance. Lornoxicam is a newer NSAID of the oxicam class for the treatment of anti-inflammatory properties in a range of painful and inflammatory conditions, including Rheumatoid arthritis and postoperative pain. Lornoxicam Patch was prepared by the solvent casting method using HPMC various grade and Eudragit RS 100 as a polymer, PEG-400 and Tween 80 uses as plasticizer, Methanol and Dichloromethane used as solvent.

LXTMP1 showed desired % Drug Content, Thickness, Folding Endurance, Flatness, Diffusion Study, Sensitivity Study on animal and Kinetic Model Study and better than other seven batches so, it is selected optimized batch.

1. Introduction

Transdermal medication conveyance frameworks are characterized as independent, discrete measurements frames which, when connected to in place skin, convey drug, through skin, at a controlled rate to systemic course. At present, most basic type of conveyance of medications is oral course. While this has outstanding focal point of simple organization, it additionally has critical disadvantages; in particular poor bioavailability because of first pass and propensity to create fast blood level spikes, prompting a requirement for high and/or successive dosing, which can be both expense restrictive and also awkward definitions on skin can be arranged into two classes as per target site of activity of containing medications. One has systemic activity after medication uptake from cutaneous micro vascular system, and different shows neighborhood impacts in skin. [1-5]

Lornoxicam is a new non-steroidal anti-inflammatory agent (NSAIDs) of oxicam class with analgesic and anti-pyretic properties. Lornoxicam used for the treatment of anti-inflammatory properties in a range of painful and inflammatory conditions, including Rheumatoid arthritis and postoperative pain. Lornoxicam is absorbed rapidly and almost completely from gastrointestinal tract. Top plasma focus is achieved inside 2.5 hrs. It has a generally short plasma half-life (3 to 5 hrs.). Bioavailability of Lornoxicam is 90-100 %. [6]

The prime objectives were to develop Transdermal matrix patch that:

1. To localize drug into systemic compartment devoid of being absorbed to avoid systemic side effects.

2. To control/modified release of drug at specific site and hence dose and dose frequency can be decrease thereby obtaining great therapeutic effectiveness.

2. Materials and Method

2.1 Materials [7-15]

Lornoxicam was obtained from Ethicare pharma. pvt. Ltd. HPMC K-4, K-15, K-100 was obtained from Signet chem. Itd, Goa. Eudragit RS-100 was obtained from Signet chem. Itd. Mumbai. Ethyl cellulose, Chitosan, Polyethylene glycol-400, Tween 80, Methanol, Dichloromethane were obtained from Sulab (Pioneer sales). Baroda.

2.2 Method of preparation

2.2.1 Formulation of transdermal matrix patch by using solvent Casting Method: [16-17]

The transdermal matrix patches will prepared by using solvent casting method. Required amount of plasticizer was added to polymer dispersion. Drug was dissolved to form aqueous solution with constant stirring for 30 minutes with adequate clarity and mixed in above dispersion. Solution was casted in a glass Petri dish (previously lubricated with glycerin) having diameter range of 7-8 cm and thickness 0.3-0.5 mm. Then it was dried at room temperature. It was approximately 24 hours to dry at room temperature; Dried TDDS was carefully removed from Petridis and was cut into size required for Evaluation.

3. Evaluation of transdermal patch

3.1. Physicochemical evaluation: [18-25]

3.1.1. Thickness:

The thickness of drug prepared patch is measured by using a digital micrometer at different point of patch and determines average thickness and standard deviation for same to ensure thickness of prepared patch.

3.1.2. Weight Uniformity:

A specified area of patch is to be cut in different parts of patch and weigh in digital balance. Average weight and standard deviation values are to be calculated from individual weights.

3.1.3. Drug content Determination:

An accurately weighed portion of film (above 100 mg) is dissolved in 100 mL of Phosphate buffer in which drug is soluble and then solution is shaken continuously for 24 hrs. in shaker incubator. Then whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically.

3.1.4. % Moisture Content:

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 hrs. Films are weighed again after a specified interval until they show a constant weight. % moisture content is calculated using following formula.

$$\boldsymbol{Moisture\ content} = \frac{\boldsymbol{Initaial\ wt - Final\ wt}}{\boldsymbol{Final\ wt}} * \mathbf{100}$$

3.1.5. % Moisture uptake:

Weighed film sare kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

$$\boldsymbol{Moisture\ Uptake} = \frac{\boldsymbol{Final\ wt. - Intial\ wt}}{\boldsymbol{Intial\ wt}} * \mathbf{100}$$

3.1.6. Flatness: [40]

Three longitudinal strips are to be cut from each film at different portion. Length of each strip was measured and variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

3.1.7. Folding Endurance:

Folding endurance is determined by repeatedly folding film at same place until it break. Number of times films could be folded at same place without breaking is folding endurance value.

3.1.8. Tensile Strength:

The tensile strength was determined by using a modified pulley system. Strip of patch (2*2 cm^2) was cut and set between these two clamps. Weight was gradually increased on pan, so as to increase pulling force till patch broke. Force required to break film was consider as a tensile strength (kg/cm^2).

Tensile strength=F/a x b (1+L/l)

Where, F = force required to break;

a=width of film;

b = thickness of film;

L = length of film;

l =elongation of film at break point.

3.1.9. Flux and Permeability coefficient:

The flux (mg cm^{-2} hr^{-1}) of Lornoxicam was calculated from slope of plot of cumulative amount of Lornoxicam permeated per cm^2 of skin at steady state against time using linear regression analysis. Steady state permeability coefficient (Kp) of drug through rat epidermis was calculated by,

Kp = J/C

Where *J* = flux

C = concentration of Lornoxicam in patch.

3.1.10. In-vitro Permeation study

An *in-vitro* permeation study can be carried out by using diffusion cell receptor compartment capacity of 12 ml. excised cellophane paper was mounted between donor and receptor compartment of diffusion cell. Formulated patches were placed over paraffin film. Receptor compartment of diffusion cell was filled with phosphate buffer pH 7.4. Whole assembly was fixed on a magnetic stirrer, and solution in receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; temperature was maintained at 32 ± 0.5 °C.

3.1.5.11. Kinetic Analysis of Release Data: [26-29]

Table 1: Release Kinetic Mechanism

Release Exponent 'n'	Drug Transport Mechanism	Rate as a function of Time
0.5	Higuchi Matrix	$t^{n-0.5}$
0.5<n<1.0	Non- Fickian Diffusion	t^{n-1}
1.0	Zero Order Release special Case–II Transport	Zero Order Release
Higher release (n>1)	Super Case–II Transport	t^{n-1}

3.1.5.12. Solvent Residual Analysis

Solvent Residual Analysis was done to determine organic solvent residual traces present in Transdermal Patch of used as Casting solvent.

3.1.5.13. Skin irritation Study:

Animals to be required

1. Species/ Common Name: Wistar rats
2. Weight: 150-200 grams
3. Gender: Male

Table 2: Protocol of skin irritation study

Groups	Route of drug administration	No. of Animals
Skin irritation studies		
Group-I: Control (Topical patch without drug)	Topical	**6**
Group-II: Standard Marketed conventional Diclofenac Patch	Topical	**6**
Group-III: Optimized Lornoxicam Patch loaded Topical Gel formulation	Topical	**6**

Procedure:

Skin irritation and sensitization testing can be performed on healthy wister albino rats. rats were divided into three groups of six rats in each group. dorsal surface ($4cm^2$) of rats were cleaned and remove hair from clean dorsal surface by shaving and clean surface by using rectified spirit and representative formulations can be applied over skin. patch is to be removed after 24 hrs and skin was observed and classified into 5 grades on basis of severity of skin injury.

3.1.5.14. Stability study

Stability studies will carried out for optimized patch formulation at Room Temperature for 1 month. samples were withdrawn at 0, 10, 20, 30 days and evaluated for Drug Content and *in*-vitro diffusion study.

4. Result and discussion

4.1. Dose of Drug and Loading Dose Calculation:

4.1.1. Dose of Drug:

Dose of drug = (ORAL DOSE * ORAL BIOAVABILITY/ BODY SURFACE AREA) / 100

Where oral dose of drug (Lornoxicam) =8 mg

Oral bioavability = 90%

Body surface area = 1.73 cm^2

Dose of Drug = 4 mg

4.1.2. Drug Loading Calculation:

1. Average Patch Size= 21.2 cm^2
2. Dose of Drug (Lornoxicam) = 4 mg

   4 cm^2 (2 cm X 2 cm) of Patch = 4 mg of Drug (Lornoxicam).

   So, 21.2 cm^2 of petri plate size = (?) mg of Drug (Lornoxicam) require.

   = 4 X 21.2 / 4

   = 21.2 mg of Drug (Lornoxicam) in 21.2 cm^2 of P.P.

Table 4: Batch Design

Code	Drug (mg)	HPMC k4M (mg)	HPMC k15M (mg)	HPMC k100M (mg)	Eudragit RS 100 (mg)	PEG-400: Tween 80	Solvent	Total
LXTMP 1	8	250	-	-	-	1:0.5	1:4	20ml
LXTMP 2	8	300	-	-	-	1:0.5	1:4	20ml
LXTMP 3	8	-	250	-	-	1:0.5	1:4	20ml
LXTMP 4	8	-	300	-	-	1:0.5	1:4	20ml
LXTMP 5	8	-	-	250	-	1:0.5	1:4	20ml
LXTMP 6	8	-	-	300	-	1:0.5	1:4	20ml
LXTMP 7	8	-	-	-	250	1:0.5	1:4	20ml
LXTMP 8	8	-	-	-	300	1:0.5	1:4	20ml

4.5. Characterization of Developed Transdermal patch:

Table 5: Physico-chemical evaluation

Batch Code	Parameter(n = 3)				
	Thickness (mm) ± S.D	Weight uniformity (gm) ± S.D.	Drug content (%)± S.D.	Folding Endurance ±S.D.	Flatness (%) ±S.D.
LXTMP 1	0.27±0.06	0.246±0.0045	93.3±1.93	65.00±4.58	90±2.52
LXTMP 2	0.26±0.04	0.294±0.0021	95.4±2.08	68.33±6.03	96±1.53
LXTMP 3	0.29±0.03	0.252±0.0020	91.2±3.39	78.33±2.52	91±4.51
LXTMP 4	0.32±0.03	0.299±0.0026	93.0±2.57	72.67±2.52	93±1.53
LXTMP 5	0.34±0.04	0.254±0.0010	90.0±4.70	70.33±5.03	94±4.04
LXTMP 6	0.33±0.03	0.302±0.0030	92.4±1.87	70.67±3.06	89±4.16
LXTMP 7	0.37±0.05	0.242±0.0065	94.2±1.00	73.33±9.02	92±2.52
LXTMP 8	0.40±0.06	0.295±0.0055	92.4±1.91	70.00±2.00	91±3.51

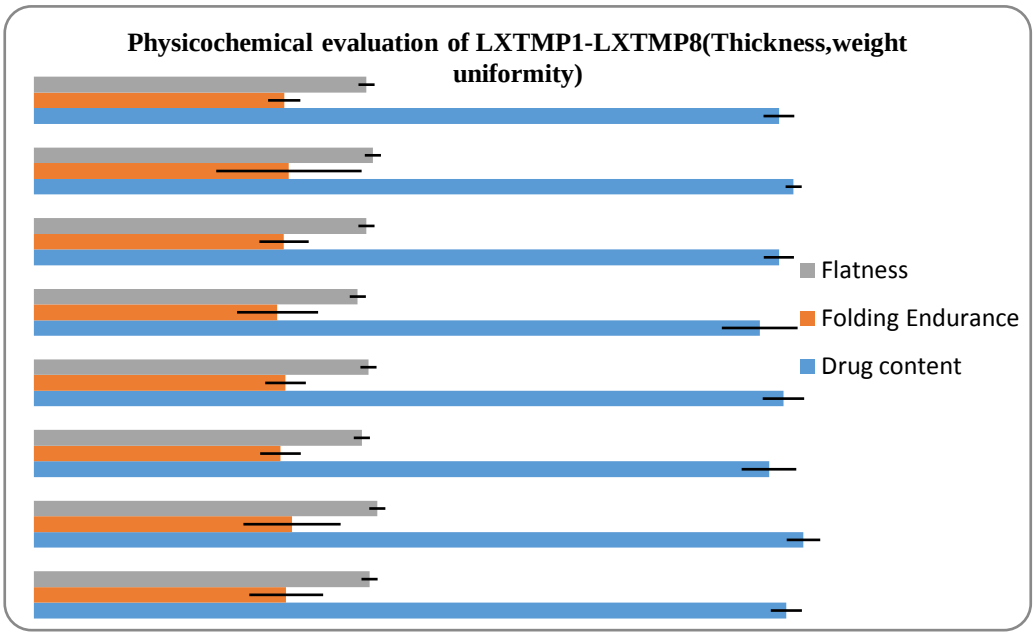


Figure 1: Physicochemical evaluation of LXTMP1-LXTMP8 (Thickness, weight uniformity)

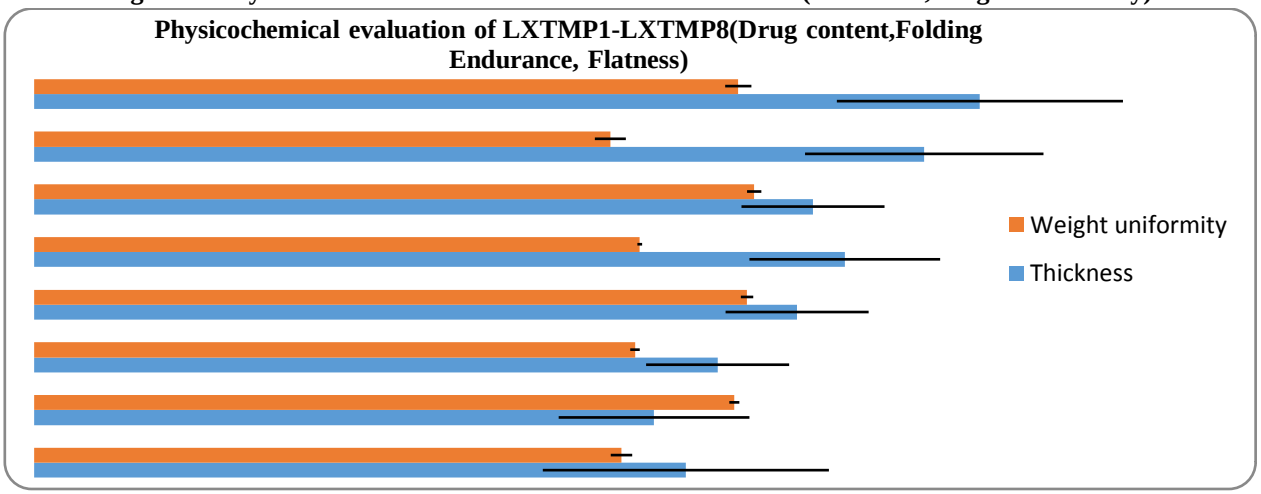
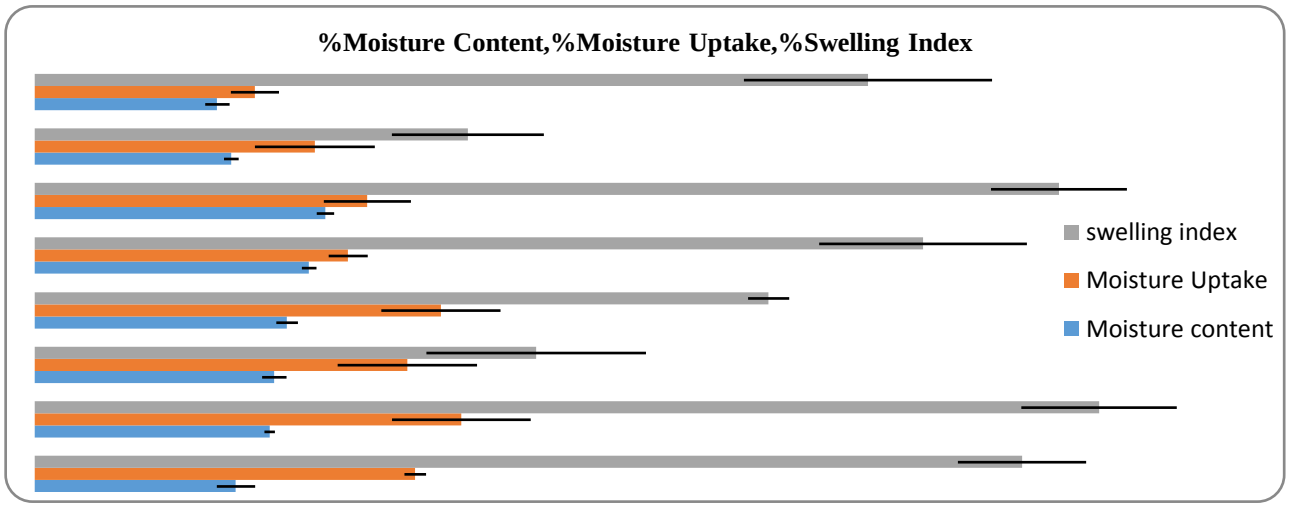


Figure 2: Physicochemical evaluation of LXTMP1-LXTMP8 (Drug content, Folding Endurance, Flatness)

Table 6: Tensile Strength, % Swelling Index, Moisture Uptake and Moisture Content

Batch Code	Parameter(n = 3)			
	Tensile Strength (Kg/cm^2) ± S.D.	Swelling Index % ± S.D.	%Moisture Content ± S.D.	% Moisture Uptake ±S.D.
LXTMP 1	2.3±0.153	28.32±1.84	5.8±0.55	10.9±0.31
LXTMP 2	2.5±0.252	30.53±2.23	6.7±0.15	12.2±1.99
LXTMP 3	2.7±0.300	14.38±3.15	6.9±0.35	10.7±2.00
LXTMP 4	3.1±0.351	21.05±3.59	7.2±0.31	11.6±1.71
LXTMP 5	3.4±0.058	25.48±2.98	7.9±0.21	9.0±0.56
LXTMP 6	3.6±0.208	29.38±1.95	8.3±0.25	9.5±1.25
LXTMP 7	4.2±0.252	12.42±2.18	5.6±0.21	8.0±1.72
LXTMP 8	4.3±0.200	23.90±3.56	5.2±0.35	6.3±0.69

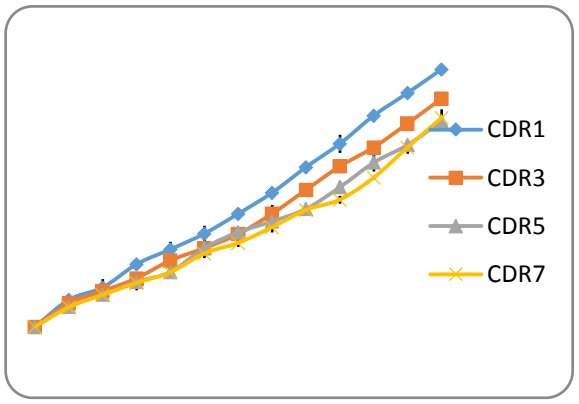


4.5.3. *In*-vitro permeation study:

Figure 3: *In*-vitro permeation study

Table 7: *In*-vitro permeation study

Time (Hrs)	% Cumulative drug release (n=3)							
	LXTMP 1± S.D	LXTMP 2± S.D	LXTMP 3± S.D	LXTMP 4± S.D	LXTMP 5± S.D	LXTMP 6± S.D	LXTMP 7± S.D	LXTMP 8± S.D
0	0	0	0	0	0	0	0	0
1	6.47±1.20	6.06±1.25	5.66±1.63	5.42±0.54	4.85±0.43	4.69±0.45	4.69±0.91	4.77±0.65
2	9.43±0.98	9.16±2.34	8.56±0.87	7.73±0.35	7.76±1.12	7.67±0.21	7.67±1.02	6.70±2.12
3	15.03±1.23	13.36±1.54	11.66±1.24	10.76±1.24	10.80±2.01	10.54±1.24	10.54±0.64	9.98±0.90
4	18.60±1.85	18.57±1.24	15.93±1.14	15.77±0.85	13.15±1.32	13.11±2.01	13.11±0.37	14.13±0.56
5	22.37±1.94	23.25±2.05	18.87±0.95	17.74±1.12	18.95±1.04	17.61±1.52	17.61±1.09	17.92±0.74
6	27.16±1.24	25.86±0.84	22.28±1.24	20.42±0.97	22.72±0.62	24.19±1.92	20.15±0.92	21.29±0.83
7	32.21±0.68	31.21±0.94	27.16±2.14	25.82±0.52	25.32±0.78	25.31±0.64	23.92±1.23	25.56±0.25
8	38.34±1.25	37.28±0.24	32.88±1.52	30.73±1.34	28.34±0.24	28.32±0.72	28.06±0.64	28.77±1.63
9	44.00±2.18	42.87±0.67	38.54±0.64	33.90±2.12	33.56±1.39	31.21±1.02	30.55±0.95	31.87±1.02
10	50.74±1.40	48.73±0.84	43.11±0.38	39.60±1.56	39.49±2.14	36.77±0.64	35.86±0.46	35.16±0.56
11	56.20±1.34	53.25±1.07	48.84±0.74	46.00±2.04	43.71±1.14	41.68±0.53	43.15±1.52	41.88±0.95
12	61.86±0.87	58.71±1.13	54.83±1.04	51.12±1.87	49.47±1.37	47.14±1.34	50.22±2.08	46.97±1.59



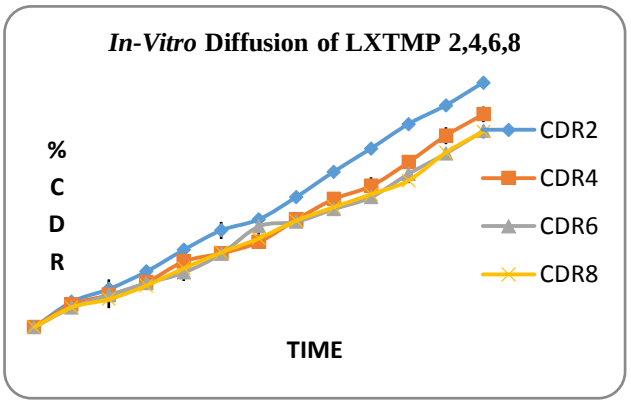


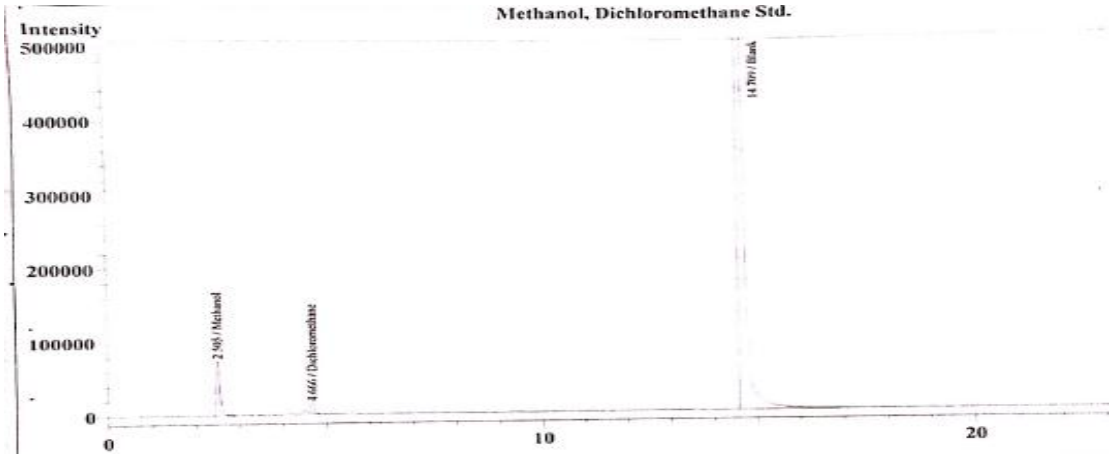
Table 8: Flux and permeability co-efficient

Time (hrs)	Batch F1	
	Flux *J* (mg/cm2/hr)	Permeability co-efficient (kP)
0	0.000	0
1	0.793	0.037393
2	0.773	0.03646
3	0.014	0.000654
4	0.006	0.00028
5	0.007	0.000354
6	0.010	0.000472
7	0.010	0.000472
8	0.013	0.00059
9	0.174	0.008203
10	0.217	0.010254
11	0.130	0.006153
12	0.083	0.003931

Table 9: Kinetic analysis of release data

Model	Zero-Order	First-Order	Hixson-Crowell	Korsmeyer-Peppas	Higuchi
R^2 value	**0.992**	**0.874**	**0.965**	**0.751**	**0.945**
Slope	**5.415**	**0.113**	**0.568**	**0.901**	**0.042**
Intercept	**-0.321**	**0.675**	**1.784**	**-0.782**	**0.790**

4.5.6 Solvent Residual:



4.5.7. Skin irritation study

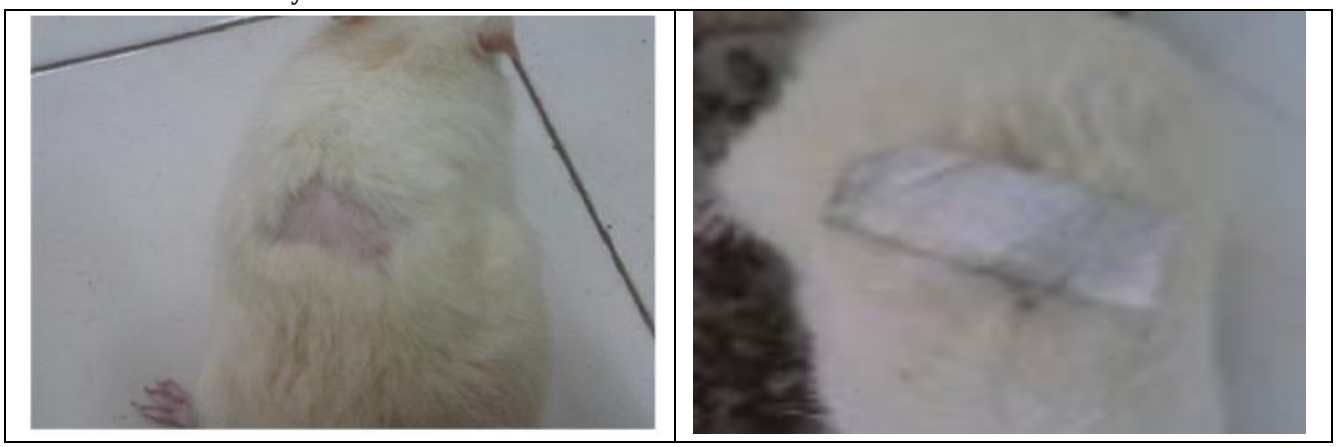


Figure 4: Skin irritation study

4.5.8. Stability Study

Table 11: Stability Study

Temperature/ Humidity condition	Time (Days)	Drug Content (%)		*In-vitro* drug release (%)	
		Initial± S.D	Final± S.D	Initial± S.D	Final± S.D
	0	93.3±1.12	93.5±0.95	61.8±1.56	60.3±1.02
	10	93.3±0.85	93.4±0.112	61.8±2.03	60.5±2.31
Room Temperature	20	93.3±0.94	93.3±0.34	61.8±0.78	61.5±1.16
	30	93.3±1.24	93.1±0.84	61.8±1.26	61.7±0.94

5. Summary and conclusion

Transdermal therapeutic systems are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver drug(s), through skin, at a controlled rate to systemic circulation. By development of transdermal matrix patch of Lornoxicam using HPMC and Eudragit RS-100 as release controlling polymers and Dichloromethane: Methanol (1:4) as solvent, increases permeability and bioavailability of Lornoxicam and increase patient compliance. All formulations showed acceptable physiochemical characteristics i.e. appearance, thickness, folding endurance, moisture content. From identification tests such as Ultra violet visible spectroscopy, Infrared spectroscopic study, melting point, partition co-efficient it was conclude that drug sample is Lornoxicam with acceptable purity grade. Partition coefficient Value shows that Lornoxicam possess sufficient lipophilicity. A low concentration of Plasticizer gives a rigid and brittle polymeric film. So plasticizer is required to improve mechanical property. HPMC and Eudragit RS-100 both are hydrophilic polymers in nature. As molecular weight of polymer increases viscosity also increase. Elasticity and elongation is more in HPMC higher percentage than Eudragit. *In*-vitro permeation study shows that formulation of LXTMP 1 batch with HPMC K- 4 M shows more sustained release of drug during 12 hrs study

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