How to Cite:
Kapoor, B., Bhatt, S. P., Bilandi, A., Sahiba, S., Singh, B., & Kumar, P. (2022). Development, characterization and in VIVO evaluation of diffusion controlled transdermal matrix patches of a model anti-Inflammatory drug. *International Journal of Health Sciences*, *6*(S7), 2875–2890.
https://doi.org/10.53730/ijhs.v6nS7.12141

Development, characterization and *in VIVO* evaluation of diffusion controlled transdermal matrix patches of A model anti-Inflammatory drug

Bhawana Kapoor*
Assistant Professor, Maya College of Pharmacy, Dehradun, Uttarakhand India
Phone No: +91-98088667851
*Corresponding author email: kapoorbhawana.pharma@gmail.com

Sarswati Prakash Bhatt
Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, Uttarakhand, India

Ajay Bilandi
College of Pharmacy, RIMT University, Mandi Gobindgarh, Punjab, India

Sahiba
Maya College of Pharmacy, Dehradun, Uttarakhand, India

Balraj Singh
College of Pharmacy, RIMT University, Mandi Gobindgarh, Punjab, India

Parveen Kumar
Sri Ram College of Pharmacy, Karnal, Haryana, India

***Abstract*---**In the current research, diffusion controlled transdermal matrix patches of Lornoxicam, an anti-inflammatory drug was developed by solvent casting method using hydrophilic and hydrophobic polymers in different ratios and tween-80 and span-80 as permeation enhancers. Formulated patches were characterized for different physicochemical parameters in terms of moisture loss, drug content, film thickness and strength, uptake and loss of moisture, transmission of water vapor etc. All of these parameters were found be satisfactory. *In-vitro* diffusion studies of formulated patches were performed by using Franz diffusion cells. The drug diffusion rate followed zero order kinetics with super case II transport diffusion. Based on *In-vitro* diffusion data, best formulation was selected and used further for the stability analysis. Developed patches were stable

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 April 2022, Manuscript revised: 18 June 2022, Accepted for publication: 27 July 2022

at different temperature and humidity settings in terms of physicochemical properties and drug content. The optimized patches were also evaluated for the *in-vivo*anti-inflammatory and analgesic activity using suitable animal models. The results of all the *in*-vitro and in-*vivo* studies justify the selection of transdermal route for the systemic delivery of Lornoxicam to overcome its shortcomings when administered orally.

***Keywords*---**Transdermal, Lornoxicam, drug diffusion, anti-inflammatory, analgesic activity, matrix patches.

Introduction

Non steroidal anti-inflammatory drugs (NASIDs) are the class of drug used to treat fever, pain and inflammation. However NSAIDs are most commonly administered via oral route, various gastrointestinal side effects or adverse drug reactions are associated with its oral administration. The anti-inflammatory effect of NASIDs is due to the inhibition of cyclooxygenase (COX) enzyme that converts arachidonic acid into prostaglandins that is involved in promotion or modulation of pain and inflammatory responses. Inhibition of COX causes loss of gastro protection and thus results in several GI complications.

Lornoxicam is an extremely potent NSAID that is commonly used for effective control of arthritic pain and inflammation, also in relieving the pre/post operative pain associated with different surgeries [1]. The drug requires frequent oral administration due to its rapid elimination and thus modulates well known gastrointestinal side effects of NSAIDs ranging from mild dyspepsia, heartburn to ulcer and bleeding [2]. To overcome these shortcomings of lornoxicam from conventional routes of administration, it can be formulated into transdermal drug delivery system (TDDS) [3]. The drug also possesses all the ideal characteristics to be formulated into a TDDS so in the present study, we made an attempt to develop diffusion controlled matrix type transdermal patches of Lornoxicam [4-6].

Materials and Methods

Lornoxicam was obtained as a gift samples from Intas Pharmaceuticals Ltd., Dehradun (Uttarakhand). HPMC and cellulose acetate were procured from Leo chem. (Bangalore, India) and Otto kemi (Mumbai, India), respectively. Tween-80 and span-80 were procured from Otto kemi (Mumbai, India). Analytical grade excipients and solvents were used in the study.

Preparation of drug free and drug loaded transdermal films

The drug free and drug loaded transdermal films were prepared with solvent casting method using mercury as a substrate. Total 6 batches of drug free films (table 1) and18 batches of drug loaded films (table 2) were formulated using different polymers with or without permeation enhancers (5% w/w tween-80 and span-80). Polymers (1.5% w/v and 2.0% w/v) and plasticizer (30% w/w of polymers) were dissolved in a suitable solvent system (chloroform:

dichloromethane: ethanol in a ratio of 2:2:1) using magnetic stirrer [7]. The drug (0.072% w/v) was slowly added and dissolved to the above solution by constant stirring. Prepared solution was poured over mercury surface in a petriplate [8]. Rate of evaporation was controlled by covering the petri plates were with inverted funnels. After 24 hrs of drying, patches were stored at room temperature by cutting and wrapping in aluminum foil [9].

Table 1
Composition of drug free transdermal films

S. No.	Formulation code	Polymer(s)	Polymer conc. (% w/v)	Plasticizer PPG (% w/w)*
1.	F1	HPMC K4M	1.5	30
2.	F2	HPMC K4M	2.0	30
3.	F3	HPMC K100M	1.5	30
4.	F4	HPMC K100M	2.0	30
5.	F5	Cellulose acetate	1.5	30
6.	F6	Cellulose acetate	2.0	30

*Based on polymer weight

Table 2
Composition of drug loaded transdermal films

S.No.	Formulation code	Polymer(s)	Polymer (%w/v)	PPG (%w/w)*	Permeation enhancer (%w/w)*
1	A1	HPMC K4M	1.5	30	–
2	A1T	HPMC K4M	1.5	30	Tween-80
3	A1S	HPMC K4M	1.5	30	Span-80
4	A2	HPMC K4M	2.0	30	–
5	A2T	HPMC K4M	2.0	30	Tween-80
6	A2S	HPMC K4M	2.0	30	Span-80
7	B1	HPMC K100M	1.5	30	–
8	B1T	HPMC K100M	1.5	30	Tween-80
9	B1S	HPMC K100M	1.5	30	Span-80
10	B2	HPMC K100M	2.0	30	–
11	B2T	HPMC K100M	2.0	30	Tween-80
12	B2S	HPMC K100M	2.0	30	Span-80
13	C1	Cellulose Acetate	1.5	30	–
14	C1T	Cellulose Acetate	1.5	30	Tween-80
15	C1S	Cellulose Acetate	1.5	30	Span-80
16	C2	Cellulose Acetate	2.0	30	–
17	C2T	Cellulose Acetate	2.0	30	Tween-80
18	C2S	Cellulose Acetate	2.0	30	Span-80

*Based on polymer weight

Physicochemical characterization of films

Formulated films were characterized for the following physicochemical parameters [10].

Thickness

A micrometer is used to measure the thickness of the formulated patches.

Weight uniformity / variation

Weight uniformity or variation was calculated by taking weight of five film units of each formulation and their average was considered as the weight of the film.

Tensile strength

Tensile strength of the developed patches was measured by using tensile strength instrument. A small film strip was cut with a sharp blade on a glass plate and fixed between two clips of the apparatus and a pulley system with gradual increase in weight exerted the pulling force to break the film. Film elongation with the increased pulling force was recorded by the pointer as it travelled a specific distance on the scale before breaking of the film [11]. The formula for calculating the tensile strength was:

$$Tensilestrength = \frac{Breakforce}{ab}\left(\frac{1 + \Delta l}{L}\right)$$

Where,

Break force is the weight required to break the film (kg)

a and b are width and thickness of strip respectively while L is the strip length
Δl is the elongation at break

Percentage moisture absorption and moisture loss

Accurately weighed films were kept in the desiccator. Saturated aluminum chloride solution of 80% RH was used as a desiccant. After 3 days, films were taken out and reweighed. Formula used to predict the amount of moisture absorbed is:

$$Moistureabsorption\ (\%) = \frac{Finalweight - Initialweight}{Initialweight} \times 100$$

Percentage moisture loss was also calculated using the same formula while the desiccant used was anhydrous calcium chloride.

Water vapor transmission rate

The moisture that is transmitted per unit time through per unit patch area is used for assessing the permeation characteristics of formulated patches. Properly washed dried glass transmission cells filled with a desiccant (1 gm of fused anhydrous $CaCl_2$) were used. Transdermal films were fixed above the rim of the

transmission cells. The pre weighed cells were stored using potassium chloride saturated solution of 80% RH in a closed desiccator. After 24 hrs of storage, the cells were removed and reweighed. Water vapor transmission rate was then calculated as the ratio of WL/S, where W is the gm of water transmitted per 24 hrs, L is the patch thickness (cm) and S is the surface area in cm^2.

Folding endurance

Folding endurance was determined to predict the plasticizer's efficiency and the strength of formulated patches. It is calculated by folding the film at the same place number of times till the development of visible cracks or breaking.

Swellability

Pre weighed transdermal films were allowed to swallow in a petriplate containing 10 mL of distilled water. Increase in weight was measured at regular time intervals, till a constant weight was attained. Swellability (S) was determined as the ratio of difference in weight (difference in weight at time t and time zero) to the initial weight.

Drug content uniformity

The film was dissolved in 5 mL of casting solvent, later diluted to 10 mL with pH 7.4 phosphate buffer. After 30 minutes stirring resulting solutions were rediluted with pH 7.4 phosphate buffer and filtered. A blank was prepared in the same manner using drug free patches to neglect the absorption of formulation components. After filtration, the drug content was determined spectrophotometrically at 378 nm [1, 12].

***In-vitro* skin permeation studies**

In-vitro skin permeation study, Franz diffusion cell was used. Phosphate buffer (pH 7.4) was used to fill the receptor compartment of the diffusion cell and a cellophane membrane was placed between the donor and receptor compartments. Prepared transdermal film was mounted on the cellophane membrane and covered with aluminum foil. This whole assembly was maintained at 37 ± 1°C with continuous stirring using a magnetic stirrer. 1 ml of sample was withdrawn at constant time interval and replaced with the equal volume of diffusion medium. Spectrophotometric analysis of the samples was made at 378 nm for determining drug content [13].

Drug release kinetics

The Drug release rate and mechanism of the formulated transdermal films were determined by fitting the diffusion data into various kinetic equations like zero-order equation, first-order equation, higuchi's equation and korsmeyer-peppas equation. Analysis of different diffusion release mechanism is based on the values of rate (as a function of time) and release exponent [14].

Skin irritation study

Formulated patches were evaluated for skin irritation/sensitization in mice. Two groups of mice (each group having 6 mice) were used for the study, one as a control and other as a test group [15]. Control group was treated with placebo patch (without drug, 2.0×2.0 cm^2), while the test group was treated with formulated patches of lornoxicam (2.0×2.0 cm^2). Each patch was removed after 24 hrs of exposure, and the application sites were examined and scored for signs of erythema and edema as per Draize test [16-18].

Biological activities

Anti-inflammatory activity

The anti-inflammatory effect of selected optimized transdermal formulation was determined using carrageenan – induced paw edema in male rat [19-21]. The rats were divided into two groups (6 mice in each group). Control group received no treatment prior to the inflammation induction while the test group was treated with formulated patches of lornoxicam to the abdominal area 6 hrs prior to the carrageenan injection. Twenty micro liters of 3% solution of carrageenan in normal saline was injected into the sub planter region in the right hind paw of the rats of both groups [22].The left hind paw (control) was injected with the same amount of normal saline. Thus we achieved two controls for each rat and for entire treatment group. The paw volume was measured immediately after carrageenan injection and hourly up to 3 hrs using plethysmometer. Degree of paw swelling in both the groups was calculated as:

$$\%\, Swelling = \frac{V_t - V}{V} \times 100$$

Where V_t is the mean volume of carrageenan injected paw and V is the mean volume of saline injected paw. The average paw swelling was compared between the control and test group and the percent inhibition of the edema formation was determined using following formula:

$$\%\, Edemainhibition = \left(1 - \frac{S_t}{S_c}\right) \times 100$$

Where S_t and S_c are the percent swelling of drug treated group and the control group respectively.

Analgesic activity

Analgesic activity of lornoxicam transdermal patches was evaluated with a writhing test. The mice were divided into two groups (each group with 6 mice). Control group received no treatment prior to the induction of writhing response [23]. The animals of the test group were treated with transdermal patches of lornoxicam (2.0×2.0 cm^2) to the abdominal area, 12 hrs prior to the acetic acid injection. 10 mL/kg of 0.8% v/v acetic acid is injected via intraperitoneal route to induce the writhing response. Total numbers of writhing were counted to measure

the nociception intensity[24]. The mean writhing number was obtained for each group and percent analgesic activity was calculated by the following formula:

$$\%\ Analgesicactivity = \left(1 - \frac{N_t}{N_c}\right) \times 100$$

Where N_t and $N_{c\ are}$ the mean writhing numbers of test group and control group respectively.

CPCSEA guidelines were strictly followed for performing all the experiments of *in-vivo* studies (The experimental protocol was approved by the Institutional Animal Ethics Committee, Lord Shiva College of Pharmacy, Sirsa (Haryana) with protocol approval number LSCP/2010/873).

Stability analysis

The stability of the active ingredients is the major criteria for the approval or rejection of any formulation. The patches were enfolded in aluminum foil and stored at different temperatures, i.e, refrigerated, room and accelerated temperature over a period of 60 days. The patches were analyzed for the drug content and other parameters at weekly time intervals [3, 7, 25].

Results and Discussion

In the current study, transdermal matrix patches of lornoxicam were formulated using various hydrophobic polymers and hydrophilic polymers namely cellulose acetate and HPMC (K4M, K100M) by solvent casting method using mercury as a substrate. Use of mercury prevents the films to adhere to the petri dish and also produce smooth patches with drug content uniformity. Polymers were selected during the polymer screening studies as they are non-toxic, non-irritant, biodegradable and easily available. They also have the great potential for controlling the drug release.

To prevent embrittlement, PPG was tried as a plasticizer at a concentration range of 10%-40% w/w and preliminary experimental studies justified the use of 30% w/w PPG as a plasticizer to produce soft and flexible patches that can be easily detached from the mercury surface without any cracking or breaking. With the use of plasticizers, glass transition temperature gets shifted to lower value which is an important formulation factor to be considered. From the experimental, formulated patches were found to be soft with the use of plasticizer as compared to non plasticized rigid and brittle patches. Different permeation enhancers were tried to improve release profile of drug loaded transdermal patches. Tween -80 and span-80 (5% w/w) were used as permeation enhancers.

Physicochemical characterization of films

The formulated transdermal patches were characterized for various physicochemical parameters and their results are summarized in Table 3-5. The patches were smooth, uniform and flexible. Data of film thickness measurement that varied from 0.36±0.003 mm to 0.70±0.002 mm confirmed the patch

uniformity. Wight uniformity was found to be there in different batches weighing between 46.55 ±0.434 to 59.15±0.341 mg. Values of % moisture absorption and % moisture loss were found to be within the acceptable range with low standard deviation. Experimental data revealed that hydrophilic polymer, HPMC have higher value of moisture absorption and moisture loss than that of hydrophobic polymer, cellulose acetate and also both the parameters were found to be increased with increasing hydrophilic polymers concentration. Transdermal film remains stable, soft and free from complete drying with small moisture loss also the low moisture absorption protects the patches from bulkiness as well as from microbial contamination.

Table 3
Physicochemical parameters evaluated for drug free films

S.No.	Formulation code	%Moisture absorption	% Moisture loss	Water vapor transmission rate (gm/cm.24h)	Swelling index (%)
1.	F1	2.955±0.022	5.345±0.004	$10.84\times10^{-4}\pm0.44\times10^{-4}$	39.23±0.44
2.	F2	3.351±0.068	6.285±0.016	$10.37\times10^{-4}\pm0.84\times10^{-4}$	36.63±0.38
3.	F3	3.990±0.044	6.567±0.069	$8.92\times10^{-4}\pm0.36\times10^{-4}$	31.35±0.34
4.	F4	4.632±0.025	7.473±0.017	$8.61\times10^{-4}\pm0.24\times10^{-4}$	27.81±0.56
5.	F5	2.298±0.053	4.173±0.024	$5.64\times10^{-4}\pm0.55\times10^{-4}$	17.28±0.31
6.	F6	2.988±0.044	4.849±0.013	$5.34\times10^{-4}\pm0.23\times10^{-4}$	14.92±0.60

Note: All values are means ± S.D. of three determinations

Table 4
Physicochemical parameters evaluated for drug free films

S.No.	Formulation code	Thickness (mm)	Weight Variation(mg)	Tensile Strength (kg/mm^2)	Folding endurance
1.	F1	0.048±0.002	46.55±0.434	0.446±0.017	344±7
2.	F2	0.053±0.003	53.90±0.194	0.451±0.026	385±6
3.	F3	0.066±0.005	54.27±0.214	0.490±0.061	368±4
4.	F4	0.070±0.002	63.62±0.316	0.506±0.048	426±3
5.	F5	0.036±0.003	52.63±0.396	0.372±0.022	241±7
6.	F6	0.043±0.001	59.15±0.341	0.328±0.028	285±3

Note: All values are means ± S.D. of three determinations

Table 5
Drug content of transdermal patches of lornoxicam

S. No.	Formulation code	% Drug content	Cumulative % drug release
1.	A1	97.67±0.003	79.52±0.12
2.	A1T	98.68±0.003	89.36±0.06
3.	A1S	98.82±0.008	94.33±0.11
4.	A2	96.98±0.220	73.20±0.13
5.	A2T	97.93±0.005	83.15±0.09
6.	A2S	98.35±0.009	86.59±0.11
7.	B1	96.98±0.001	63.11±0.52
8.	B1T	98.85±0.004	76.36±0.23
9.	B1S	97.17±0.005	80.20±0.12
10.	B2	97.53±0.003	61.58±0.41
11.	B2T	98.32±0.003	72.81±0.07
12.	B2S	98.73±0.002	76.02±0.18
13.	C1	97.37±0.006	54.58±0.21
14.	C1T	98.97±0.002	69.18±0.27
15.	C1S	98.67±0.005	74.95±0.26
16.	C2	98.22±0.005	49.67±0.16
17.	C2T	96.98±0.006	64.98±0.11
18.	C2S	97.20±0.002	67.38±0.57

Note: All values are means ± S.D. of three determinations

The formulated patches were found to have good tensile strength ranging between 0.328±0.028 kg/mm^2 to 0.506±0.048 kg/mm^2 varying with the concentration and type of polymer. The tensile strength of HPMC patches was found to be more than the cellulose acetate patches. Folding endurance of prepared patches was found to be satisfactory (>200) and the drug content was within the range of 1.052 ± 0.071 mg to 1.176 ± 0.071 mg. Swellability of formulated patches varied between 14.92±0.60% to 39.23±0.44%. Due to more water permeation within the matrix, hydrophilic polymers showed extensive swelling. The uniformity of drug content was determined spectrophotometrically that varied between 07.77 ± 0.005 mg to 07.92 ± 0.002 mg. Minimal patch variability with drug content uniformity justified the selection of process employed to prepare the patches.

The monolithic films provided drug release up to 24 hrs. The cumulative drug release from the transdermal patches containing hydrophilic polymer was found to be at faster rate than the formulations containing hydrophobic polymer as the later reduce the solvent penetration into the patch and thus helps to retain the drug in the matrix system. The concentration and the nature of polymers also affect the drug release. Drug release decreases with increased polymer concentration. The values of percent drug permeation also found to be increased linearly with increase in viscosity grade of hydrophilic polymer HPMC. The incorporation of different permeation enhancers also affects the drug release. The cumulative amount of drug released from the transdermal patches without permeation enhancers were lower than patches with permeation enhancers. The drug release was found to be greater in patches with span-80 as compared with tween-80. These results indicated that the release of lornoxicam was affected by the chemical nature and concentration of various polymers as well as permeation enhancers. Formulation A1S appears to be the best choice of matrix in the patch development of lornoxicam. Hence, it was selected as the best formulation by virtue of its maximum drug release and skin permeation.

Kinetic modeling of drug release

The *in vitro* study data was fitted to various kinetic models in an attempt to describe the release kinetics of lornoxicam from the formulated transdermal patches. The kinetic models fitted were zero-order, first-order, higuchi and Korsmeyer-Peppas model as shown in Figure 1.

The kinetic model with highest R^2 value was selected as it indicated the linearity of dissolution data. Value of R^2 is the indication of zero-order diffusion kinetics whose mechanism is best explained by the Korsmeyer-Peppas model. The slope value of 1.0079-1.1163 (n >1) indicated super case II transport diffusion mechanism. *In-vitro* permeation profile kinetic analysis of the best formulation is shown in table 6.

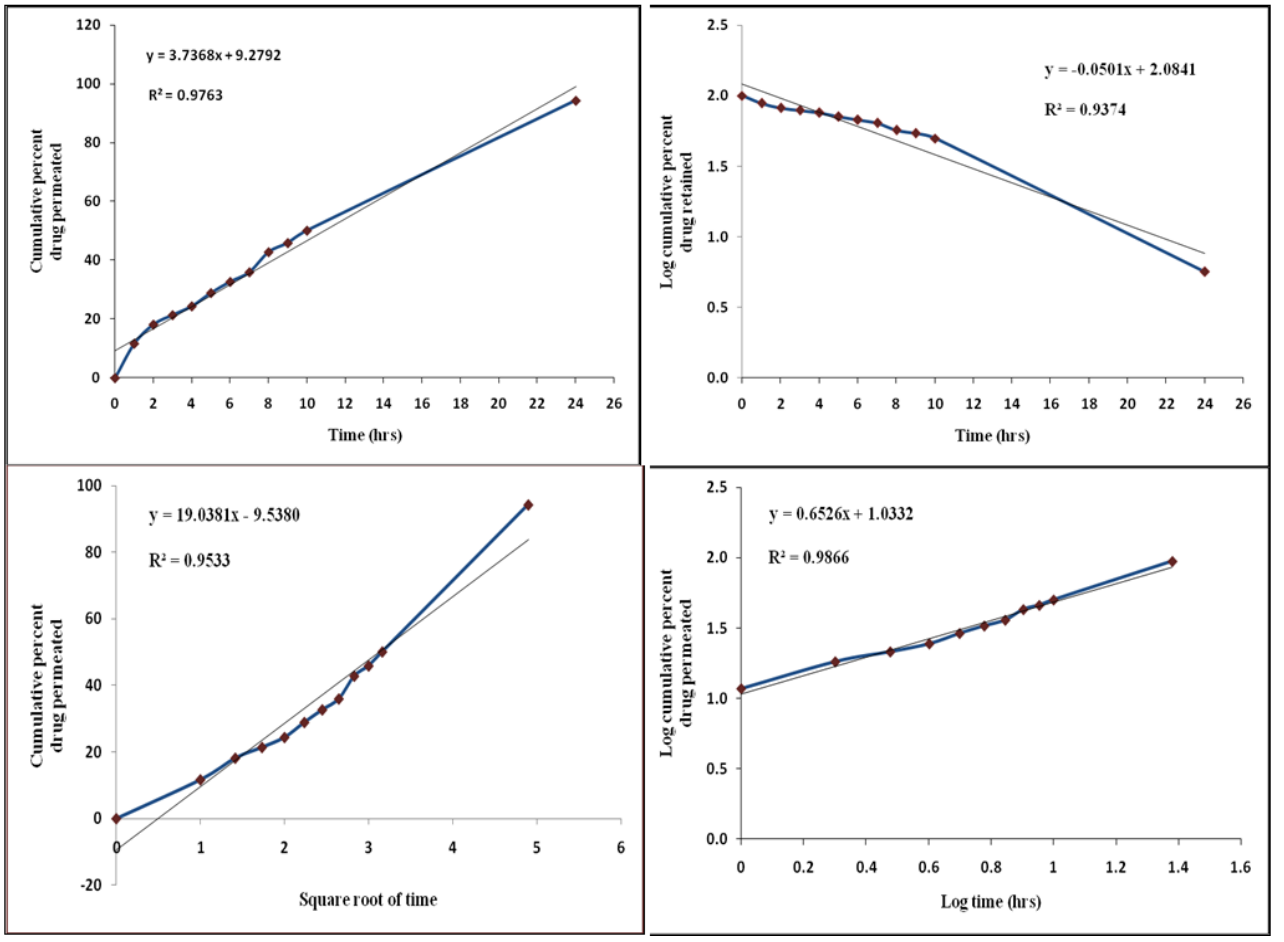

Figure 1: Kinetic analysis of drug release profile of the best formulation (A1S)

Table 6: Parameter for the kinetic analysis of formulation A1S

Kinetic Model	Slope	Intercept	R^2
Zero Order	3.7368	9.2792	0.9763
First Order	-0.0501	2.0841	0.9374
Higuchi model	19.0381	-9.5380	0.9533
Korsmeyer- Peppas model	1.0189	0.7047	0.7247

Skin irritation study

Skin irritancy study (Table 7) did not find any revealed any noticeable signs of erythema or edema on mice skin throughout the period of 24 hrs. Hence, the formulated patches were found to be compatible with the skin.

Table 7
Skin irritation scores following transdermal patch application (A1S)

Animal code	Group I* (Control)		Group II** (Test)	
	Erythema[a]	Edema[b]	Erythema	Edema
I	0	0	0	0
II	0	0	0	0
III	0	0	0	0
IV	0	0	0	0
V	0	0	0	0
VI	0	0	0	0
Average ± S.D.	**0±0**	**0±0**	**0±0**	**0±0**

* Group I was treated with placebo patch, ** Group II was treated with optimized formulation

a. Erythema scale: 0-none; 1-slight; 2- moderate; 3- moderate to severe; 4- severe

b: Edema scale: 0-none; 1-slight; 2-well defined; 3-moderate; and 4-severe

Biological activities

Anti-inflammatory activity

Paw edema was induced using carrageenan and it was observed that there was a significant difference in % swelling at 1, 2 and 3hrs. The 50.39% inhibition (statistically significant at $P < 0.01$) within 3hrs of carrageenan injection approved the tested formulation (A1S) with significantly improved anti-inflammatory activity as compared to control.

Analgesic activity

Analgesic activity was measured in mice by acetic acid induced writhing method. A significant difference was found in number of writhes between control and test group. Statistically significant writhing response with 76.18 % inhibition ($P < 0.01$) showed significantly improved analgesic activity of formulated patches as compared to control.

Stability analysis

Stability analysis was performed for the optimized patches (A1S) at different temperature conditions *viz.* 4°C, 27°C and 40°C for 2 months. The various parameters such as physical appearance, drug content and *in-vitro* drug diffusion were not significantly changed on storage which indicated that the formulations were stable at required storage conditions. The results for stability analysis are shown in table 8-9.

Table 8
Stability profile of formulation A1S at different temperatures

Time	Refrigerated temp. (4°C)			Room temp. (27°C)		
(days)	%R.D.C.	% D.R.	P.A.	%R.D.C.	% D.R.	P.A.
0	98.82±0.008	94.33±0.11	+	98.82±0.008	94.33±0.11	+
7	98.09±0.006	93.63±0.32	+	97.98±0.014	93.52±0.20	+
14	97.55±0.009	93.11±0.41	+	97.29±0.006	92.86±0.13	+
21	97.14±0.012	92.72±0.14	+	96.82±0.009	92.41±0.32	+
28	96.77±0.007	92.37±0.22	+	96.59±0.015	92.20±0.41	+
35	95.91±0.021	91.55±0.12	+	95.97±0.024	91.60±0.24	+
42	95.41±0.014	91.07±0.24	+	95.36±0.007	91.72±0.09	+
49	94.22±0.009	89.93±0.32	+	94.04±0.011	89.76±0.14	+
60	93.77±0.012	88.87±0.11	+	92.91±0.021	87.98±0.21	+

R.D.C.: Remaining drug content, D. R.: Drug release

P.A.: Physical Appearance; +: Good; -: Hard; #: Rigid, Brittle

Table 9
Stability profile of formulation A1S at accelerated temperatures

Time (days)	Accelerated temp. (40°C)		
	%R.D.C.	% D.R.	P.A.
0	98.82±0.008	94.33±0.11	+
7	96.87±0.014	92.46±0.22	+
14	96.36±0.006	91.98±0.15	+
21	95.96±0.015	91.59±0.11	+
28	93.78±0.019	89.71±0.21	+
35	92.95±0.024	88.02±0.16	+
42	92.47±0.007	88.26±0.11	+
49	91.89±0.015	87.71±0.27	+
60	90.52±0.008	86.40±0.32	+

R.D.C.: Remaining drug content, D. R.: Drug release

P.A.: Physical Appearance; +: Good; -: Hard; #: Rigid, Brittle

Conclusion

In conclusion, diffusion controlled transdermal matrix patches of lornoxicam can be formulated by solvent casting technique, using HPMC (K4M and K100M) and cellulose acetate. Nature and ratio of polymers affected the physical properties and the permeation rate. Addition of permeation enhancers profoundly increased the drug flux to the desired extent. Developed patches were found to be good with respect of their physicochemical properties. Optimized formulation A1S (with polymer HPMC K4M in 1.5% w/v along with propylene glycol as plasticizer and span-80 as permeation enhancer) has the highest drug release of 94.33% over a period of 24 hrs. Formulated patches exhibited zero order kinetics with super case II transport mechanism. Accelerated stability analysis provides a stable formulation. Skin irritation test and biological activities of the optimized formulation A1S revealed that the prepared patches are capable for the treatment of pain and inflammation with more effectiveness and better patient compliance.

References

1. Pagar R, Ghule RS, Bairagi VA, et al, 2018. Formulation and development of sustained release matrix tablets of lornoxicam. J Drug Deliv Ther. 8(2), Pages-102-6.
2. Hamza YS, Aburahama MS, 2010. Design and in vitro evaluation of novel sustained- release matrix tablets for lornoxicam based on the combination of hydrophilic matrix formers and basic pH-modifiers. Pharm Devlop Tech. 15(2), Pages- 139-53.

3. Kumar P, 2018. Solid lipid nanopartical in corporated cream of clobetasol-17-propionate: development and in-vitro evaluation. Int J Pharm Sci Res. 9(12), Pages- 5444-48.
4. Hamza YS, Aburahama, 2010. Novel sustained-release fast-disintegrating multi-unit compressed tablets of lornoxicam containing Eudragit RS coated chitosan-alginate beads. Pharm Devlop Tech.15(3), Pages- 1-15.
5. Moore N, Pollack C, Butkerait P, 2015. Adverse drug reactions and drug–drug interactions with over-the-counter NSAIDs. Ther Clin Risk Manag. 11, Pages-1061-75.
6. Ricciotti E, Garret GA, Gerald F, 2011. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol. 31(5), Pages- 986-1000.
7. Kumar P, Bhutani R, 2013. Studies on penetration enhancers in corporated cream of clobetasol-17-propionate: development and in vitro evaluation. Int J Pharm Sci Res. 4(6), Page- 2258.
8. Prabhakara P, Koland M, Ahmed MG, et al, 2010. Preparation and evaluation of transdermal patches of papaverine hydrochloride. Int J Res Pharm Sci. 1(3), Pages- 259-66.
9. Shrivastava B, Kumar P, Gupta MM, et al, 2019. Transdermal patch of timolol maleate: formulation and evaluation. APJHS. 6(1), Pages-177-88.
10. Bharkatiya M, Nema RK, Bhatnagar M, 2010. Development and characterization of transdermal patches of metoprolol tartrate. Asian J Pharm Clin Res. 3(2), Pages- 130-4.
11. Kumar PA, Shrivastava BI, Gupta MM, Sharma AK, 2019. Optimization and preparation of solid lipid nanoparticle incorporated transdermal patch of timolol maleate using factorial design. Int J Appl Pharm. 11(6), Pages- 100-7.
12. Parhi R, Suresh P, 2016. Transdermal delivery of diltiazem HCl from matrix film: Effect of penetration enhancers and study of antihypertensive activity in rabbit model. J Adv Res.7(3), Pages- 539-50.
13. Nguyen HX, Puri A, Banga AK, 2017. Methods to simulate rubbing of topical formulation for in vitro skin permeation studies. Int J Pharm. 519(1-2), Pages-22-33.
14. Romero AI, Villegas M, Cid AG, et al, 2018. Validation of kinetic modeling of progesterone release from polymeric membranes. Asian J Pharm Sci. 13(1), Pages- 54-62.
15. Ma X, Wang H, Song Y, et al, 2021. Skin irritation potential of cosmetic preservatives: an exposure-relevant study. J Cosmet Dermatol. 20(1), Pages-195-203.
16. Bharkatiya M, Nema RK, Bhatnagar M, 2010. Designing and characterization of drug free patches for transdermal application. Int J Pharm Sci Drug Res. 2(1), Pages- 35:39.
17. Park I, Dongwan K, Jindeog S, et al, 2008. Buprederm, a new transdermal delivery system of bprenorphine: pharmacokinetic, efficacy and skin irritation studies. Pharm Res. 25(5), Pages- 1052-62.
18. Laithy HME, 2009. Novel transdermal delivery of timolol maleate using sugar esters: preclinical and clinical studies. Eur J Pharm Sci. 72, Pages- 239-45.
19. Gupta GD, Gaud RS, 2006. Anti-inflammatory activity of tenoxicam gel on carrageenan induced paw-oedema in rats. Indian J Pharm Sci. Pages- 356-9.
20. Ashrafizadeh M, Najafi M, Kavyiani N, et al, 2021. Anti-inflammatory activity of melatonin: A focus on the role of NLRP3 inflammasome. Inflammation. 44(4), Pages- 1207-22.

21. ChoudharyD, Dutta KN, Kalita R, 2021. A review on transdermal patches used as an anti-inflammatory agent. Asian J Pharm Clin Res. 14(12), Pages- 21-6.
22. Baricevic D, Sosa S, Tubaro A, et al, 2001. Topical anti-inflammatory activity of Salvia officinalis L. leaves: the relevance of ursolic acid. J Ethnopharmacol. 75(2-3), Pages- 125-32.
23. Ebtsam M, Iman I, Nadia A, 2010. Formulation and stability study of chlorpheniramine maleate ransdermal patch. Asian J Pharm. 4(1), Pages- 17-23.
24. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). The COVID-19 pandemic. *International Journal of Health Sciences*, *5*(2), vi-ix. https://doi.org/10.53730/ijhs.v5n2.2937